ANNALS of ALLERGY

PUBLISHED BY THE AMERICAN COLLEGE OF ALLERGISTS

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1944

Volume 2, Number 3 Published Bimonthly

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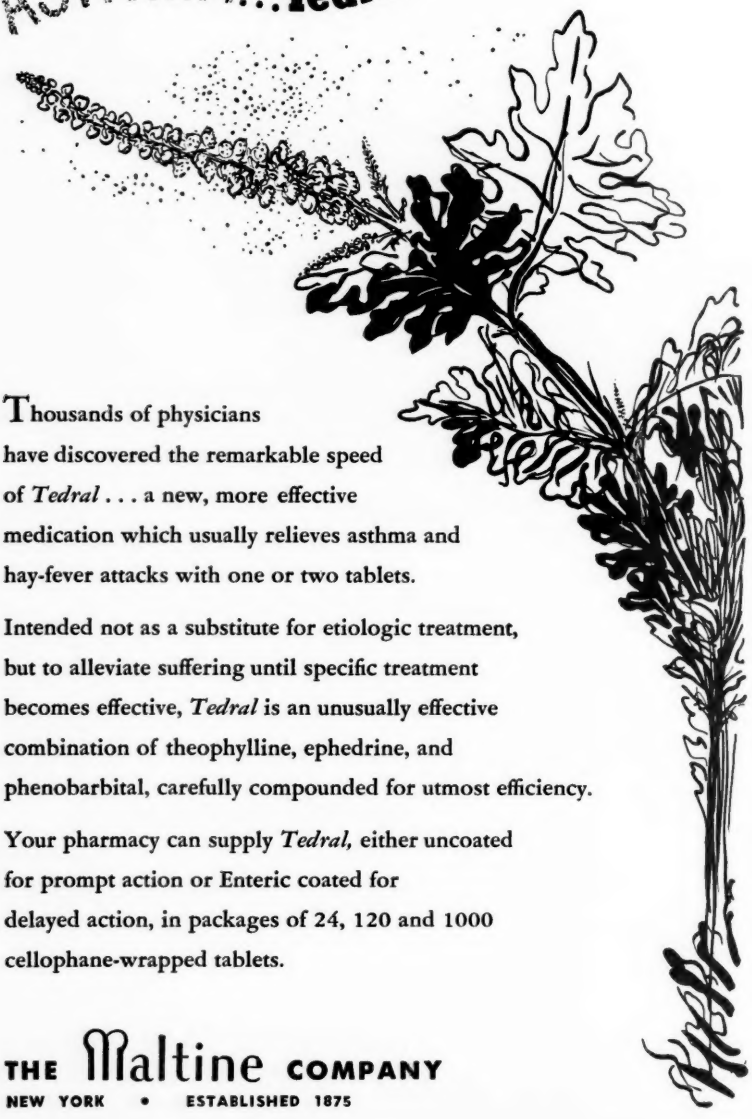

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ANNALS of ALLERGY

Published by the
American College of Allergists

Volume 2 May-June, 1944 Number 3

ALLERGY OF THE CENTRAL NERVOUS SYSTEM

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WHEN the tissue of an allergic patient comes in contact with the specific protein to which it is sensitized, a reaction, or shock, occurs. This consists in local edema, spasm of smooth muscle, or hyperactivity of glandular secretion. When this reaction occurs within the cranial cavity, the localized edema may increase intracranial pressure and simulate brain tumor, or the local anemia may cause various transient neurologic symptoms.

The recognized symptoms of increased intracranial pressure are headache, vomiting, dizziness, symptoms referable to pressure on the optic nerve, convulsions, hyperesthesia, anesthesia, paralysis and psychosis. All of these may occur as a result of an allergic shock.

It is a characteristic of allergic reactions, as best shown in asthma and angioneurotic edema, that the attacks occur periodically and between attacks the patient seems to be in perfect health. Migraine, the cause of which has previously been a mystery, fulfills these requirements. It is periodic and sudden in onset. It is characterized by severe localized headache, usually by protracted vomiting and occasionally by convulsions. Accompanying the attacks are eye symptoms of scotomata, and transient amblyopia. All suggest increased intracranial pressure. All these symptoms can be adequately explained if one presupposes a sudden angioneurotic edema of the meninges or brain substance. When the brain has been exposed during a migraine attack it has been found to be swollen and edematous. It is now ten years since Vaughan[56] proved conclusively that many cases of migraine were of allergic origin. Since then certain allergists have gone so far as to say that all migraine is allergic. In these cases, as soon as the specific allergen is ascertained and removed from the diet or the environment, the attacks disappear. The headaches can be reproduced at will by again submitting the patient to the offending protein.

A condition of interest to the neurologist is the symptom complex known as Ménière's disease, or vestibular vertigo, characterized by profound and

prolonged dizziness with or without tinnitus, and sometimes associated with prostration, vomiting and even convulsions. While this distressing disease is usually a manifestation of diseases of the semicircular canals, or the central nervous system, such as hemorrhage, tumor, or syphilis, a symptom complex indistinguishable therefrom can be caused by allergy. In 1938 Hallpike and Cairns[29] and Lindsay[43,44] have reported cases which came to autopsy in which the lesion was an edema of the semicircular canals, or as they called it "labyrinthine dropsy." Recently M. Atkinson[2,3,4,5,6] has written a number of articles on Ménière's disease. He divides it into two groups, those due to allergy the symptoms being the result of angioneurotic edema of the labyrinth, and a more frequent group due to vasoconstriction of the arteries of the internal ear. He makes the distinction by skin tests with histamine. If the reaction is positive the case is allergic and due to edema; if it is negative it is a vaso-constriction case. Various authors[26,31,47] have reported cases which proved to be due to such allergens as milk, egg, apple, orris root, horse or dog dander, and were completely relieved by the elimination of the offending material.

One such case came under my care a few years ago. A physician forty-eight years of age had carried on an active practice for twenty years. He had always been in perfect health except that he had suffered from fall hay fever for twenty years. For the previous two years he had had a feeling of drowsiness and lack of ambition in the morning and at times abdomnial distress suggesting gastric ulcer. In March, 1937, he began to suffer from dizziness, most marked in the morning and aggravated by sudden turning of the head. The symptom increased in severity until he had difficulty in driving his car and dreaded going into the operating room for fear he would be unable to complete an operation. The best medical advice available had been unable to determine the cause of his unfortunate condition or give him any relief. In June, 1937, when, fearing brain tumor, he was making his plans to go either to Johns Hopkins or the Mayo Clinic, Dr. Gage, in view of the fact that the patient had suffered from hay fever, referred him to me to see if his symptoms might possibly be due to an allergic condition.

A set of some two hundred skin tests revealed strong sensitivities to the fall pollens, barley, buckwheat, corn, flaxseed, banana, asparagus, beet, onion, parsnip, potato, spinach, string bean, tomato and turnip among the foods, and to kapok, orris root, pyrethrum and tobacco. His diet was arranged, environmental irritants eliminated and smoking forbidden. Within a few days the dizziness disappeared, his energy returned, and he is again carrying on his active practice without fear or anxiety. The results of the treatment make it certain that the Ménières symptoms, which nearly made our confrère retire from practice, was a case of cerebral allergy, and as soon as this was ascertained cure promptly followed.

The etiology of infantile convulsions, unassociated with injury or disease of the central nervous system, or with fever, have long been a

puzzle to the medical profession. Teething, indigestion, overfeeding, and worms have been cited as the underlying factors. This subject has been but slightly touched upon in the literature on allergy and no systematic allergic study has been made, though as far back as 1921 Thompson[55] of London in a study of 200 cases of infantile convulsions stated that they were usually due to poisoning by milk, cereals or eggs, the foods which are the most common factors in the production of allergic shock. From my own observations, I am convinced that at least a certain number of cases of infantile convulsions are due to allergic reactions in the central nervous system. I have seen it many times. Some years ago a child twenty-three months of age was brought to me with a history of convulsions for two months occurring several times a day. Physical examination failed to explain the convulsions. Intestinal parasites were ruled out by a therapeutic test. Skin tests, however, gave positive reactions to apple, date, beef, celery, spinach, dog hair, feathers, flaxseed and cotton. During the two weeks in the hospital, while the tests were being made, the child had from three to ten convulsions a day. With the completion of the tests, the removal of cotton and feathers from the environment and the elimination of the offending proteins from the diet, the convulsions ceased. The child remained free from convulsions during the next ten days during which it remained under observation in the hospital and has had no recurrence since.

In 1922 Ward[59] propounded the theory that epilepsy was as much a manifestation of allergy as is asthma, and he reported two cases of epilepsy due to food allergy. The next year Howell[30] reported fourteen epileptics who showed food sensitivity, whose attacks could be prevented or produced by food manipulation. The same year Wallis, Nicoll and Craig[58] of London showed that forty-six of 122 insane epileptics studied showed evidence of allergic sensitivity, and that fourteen in whom positive skin tests were found were cured. In 1927 Ward and Patterson,[60] in the study of one thousand epileptics, obtained positive skin tests in 48 per cent of them. Since then there have appeared many scattered reports of isolated cases, or small series of epileptics, showing definite evidence of an allergic etiology and a high percentage of family and personal history of allergy.[9,18,23,24,27,38,42,52,53,54,57,61,62]

In the last decade several series of instructive animal experiments were carried out by Davidoff and Kopeloff.[20,21,22] Using dogs and monkeys, they produced local allergic sensitivity over the motor areas of the brain by trephining and placing against the cerebral surface capsules containing horse serum or egg white. Control experiments were made with capsules containing saline solution. The horse serum was always placed against the left side of the brain and the egg white against the right side. Some days later intravenous inoculations of horse serum or egg white were made. When the horse serum was given, convulsions occurred on the right side of the body. When the egg white was injected, the convulsions

invariably appeared on the left side. In the control cases, there were no convulsions. Thus they proved that local allergic sensitivities could be produced in the brain of the animals which would cause convulsions when the specific allergen was introduced into the blood stream.

During the past fifteen years I have examined a large number of cases of epilepsy from an allergic standpoint, and, though my results have not been as striking as some of those previously reported, possibly due to the fact that most of them were cases of long standing in state hospitals in which marked cerebral degeneration had taken place, they have convinced me that in some cases of epilepsy there is a definite allergic etiology, and if this is discovered early enough, favorable results may be obtained. I shall cite a few examples:

The first case I studied aroused my enthusiasm to such an extent that I have pursued the study avidly ever since.[12,13,14,15,16,17]

Case 1.—M. F., ten years of age, was referred to me as a pediatrist in 1931 with a diagnosis of epilepsy. Her family history was not significant. Her father was a dairy farmer. She had asthma since infancy. The onset of her convulsions was at the age of six years. The epileptic attacks had increased in frequency for four years, until they were occurring on the average of twice a week. Though unfamiliar at the time with the work that had been done on the relation of allergy to epilepsy, I suggested that if the asthma could be cured, the epileptic attacks might become less frequent. No hopes were offered for a cure of the epilepsy. The parents agreed, and eighty skin tests were made by the scratch method with the following positive results: cattle hair +++, cottonseed ++++, radish ++ and cheese ±.

Cotton was removed from her environment, radishes, cheese and salad oils eliminated from her diet, and, as her home conditions precluded the avoidance of the hair and dander of cattle, weekly inoculations of cattle hair extract were begun on May 19, 1931, with a dose of 0.1 c.c. of a 1:100,000 dilution. These were continued weekly with increasing doses, the last dose, 0.9 c.c. of a dilution of 1:500, being given eight months later, on January 22, 1932.

The results were surprising. As the dose of cattle hair increased, not only were the asthmatic attacks relieved, but the epileptic seizures became less and less frequent, and in November, 1931, ceased entirely. Two years ago this patient, now married, brought her child to me. She told me at that time that she had had no asthma since I last saw her in 1932 and except for an eclamptic attack when her child was born, she has had no convulsions.

Case 2.—Another striking result was in the case of B. W., born in 1916. She was an only child, born by cesarian section, nursed for four months, and then given cow's milk and dextri-maltose. At the age of eighteen months she had facial eczema. She refused to eat eggs. She had numerous colds and stomach upsets. She had frequent attacks of croup. At five years she had pneumonia. Since she was three years of age she had had hay fever every fall, sometimes followed by asthma.

Since she was four years of age she had had digestive upsets, constipation, and recurrent attacks of mucous colitis.

Her epileptic attacks date from the age of ten years. During the succeeding nine years she had convulsions varying from once a month to once every three months. They always occurred in bed. She had fallen out of bed and bitten her tongue. The patient was a chronic invalid.

One hundred eighty-six skin tests were made by the scratch method with the

following results: ++++ to goldenrod, +++ to banana and asparagus, ++ to giant and short ragweed, dahlia, dandelion, cabbage, corn, garlic, onion and potato, and + to orris root, pyrethrum, tobacco, coffee, buckwheat, beet, and the pollen of mugwort and sunflower.

A diet free of the above mentioned foods was ordered, and on March 4, 1933, inoculations with giant and short ragweed, goldenrod, and dandelion were started and continued until August.

The result was that the patient that year had the first autumn free from hay fever in fifteen years, and was much improved in regard to her intestinal condition. The only convulsion she had in the next fourteen months was when, after driving for two days on her return from her summer home in Rhode Island and eating at restaurants where her dietary régime was somewhat lax, she had one mild attack. She said that for the first time in her life she considered herself to be well. After this she moved to another city, and we lost track of her.

Case 3.—This case was a trained nurse, twenty-two years old, the daughter of a physician. Her father suffers from migraine and urticaria. The family history and the past history is otherwise immaterial. For the past seven years she had suffered from attacks of petit mal, finally occurring five to seven times a day. In June, 1937, and January and March, 1938, she had major epileptic attacks.

Physical examination gave no cause for the symptoms. One hundred and sixty-five skin tests were negative except for a suspicious reaction to cheese and a delayed reaction to staphylococcus pyogenes aureus. On May 1 Rowe's egg, milk and wheat-free elimination diets were started. During the next two weeks on diet No. 1 she had seven attacks, all occurring in two days of examinations and dietary lapses. For two weeks on diet No. 2 she had no attacks. On diet No. 3 she had eleven attacks while attending a reunion when she broke her diet. Two weeks more on strict attention to diet No. 3 produced no attacks as did the next two weeks when she ate a mixture of all three diets.

At this point wheat was added to her diet and in the next two weeks she had seventeen attacks of petit mal. Two more weeks on the basic diets without the wheat showed but two attacks, but when milk was added she had fourteen petit mal and one grand mal attack in one day. The withdrawal of the milk improved the condition promptly and the addition of egg precipitated no attacks. The patient was then put through a course of oral desensitization to milk and when last seen she was drinking milk freely and having no attacks. I was about to begin desensitization to wheat when she married and move away.

It is probable that the symptom complex we know as epilepsy is a manifestation of various conditions, one of which is allergy. Foster Kennedy[36] has demonstrated that during an epileptic convulsion as in migraine there is marked cerebral edema. It is highly improbable that an allergic study will relieve all cases of epilepsy. If, however, even 10 per cent of the sufferers from this dire affliction can be cured, it will be a source of rejoicing to thousands of unfortunate and unhappy human beings.

In 1929 Foster Kennedy[34] reported a series of cases of paralysis of the arms following tetanus serum sickness. The most common muscles involved were the deltoids. Reactions of degeneration appeared and the paralysis lasted several weeks, but ended in complete recovery. During the next few years several other authors[1,8,10,28,41,48,50,63] reported similar cases, and in 1933 Doyle[30] collected forty-nine cases from the literature. To date over 100 cases have been reported. Opinions differ as to whether the lesion in these cases is an urticaria of the cerebrum or an

edema of the sheaths of the peripheral nerves. These anaphylactic reactions to serum are, of course, aggravated cases of allergic shock.

Other authors[11,33,45,49] have reported incidents in allergic cases, sometimes associated with asthma or migraine, and sometimes by themselves, where there occurred attacks of local anesthesia or paresthesis of the hands followed by temporary paralysis, in which the symptoms recovered promptly on the administration of adrenalin and could be prevented by eliminating from the diet the foods to which the patient was sensitive.

The mental effects of allergy have received very little study, though nervous symptoms are so common in association with the allergic diseases that until recently asthma, urticaria, angioneurotic edema and migraine were thought to be primarily diseases of the nervous system.

It is a matter of common experience that the asthmatic child, though amenable normally, becomes during an asthmatic seizure irritable and disagreeable in the extreme. This nervous excitability is usually considered to be the result of the discomfort of the attack getting on the child's nerves. This, to a considerable extent, is probably true, but numerous cases have been reported by Shannon[51] and other allergists in which high-strung, nervous, unruly, and disagreeable children, who showed none of the accepted manifestations of allergy, have been found to be hypersensitive to certain foods—most commonly wheat. When the offending proteins were removed from the diet, these children's mental attitude toward life has changed and in a few weeks the spoiled, irritable child has become happy, contented, and friendly.

I recently saw a surly, disobedient thirteen-year-old boy who had been expelled from four schools as incorrigible. As he had hay fever I did a complete series of allergy tests on him and found him sensitive to several foods as well as the autumn pollens. His diet was regulated and he returned to school. The family were astonished to find that he got along well in school, was happy in his work, joined the Boy Scouts and got along well with his fellow scouts.

Insomnia and excessive somnolence also have been overcome by correcting the diet in allergic patients.

Though it has been demonstrated many times that allergic shock can cause mental depression, bewilderment and even active delirium, the psychiatrist has entirely overlooked the possibility of some of the recurrent types of psychoses having an allergic background. It is to be hoped that in the near future some psychiatrist may be aroused to the advisability of making a thorough allergic study of the different types of psychosis, especially those recurring at regular intervals. The results may be negative but the possibilities are tremendous. If all psychotic patients having allergic conditions could be collected in one institution, and facilities provided for a thorough allergic study and dietetic régime, much might be accomplished.

We were deeply interested in one woman who had asthma due to dog and cattle hair. She had frequent recurrent attacks of mental confusion,

which she herself associated with her asthmatic attacks. After admission to the hospital she was much improved but had one serious mental relapse shortly after a supervisor brought a pet dog on the ward. Such incidents as these deserve careful study.

Doctor Osler once said that syphilis was a disease which could simulate any other disease in man, and that in making a diagnosis it should be considered no matter how remote the possibility appeared. The same may now be said of allergy. Allergists do not claim that all those suffering from paralysis, headache, vertigo or convulsions are allergic. They do, however, emphasize that in all these conditions allergy may be the underlying cause, and in searching for the etiology of all obscure nervous conditions allergy should be taken into consideration, and, especially when there is a family or past history of other allergic manifestations, the patient should be given the opportunity of a scientific allergic investigation.

Karnosh[32] has recently reported a case of dementia precox associated with a severe facial eczema. Following each course of insulin shock not only his mental condition improved, but the eczema cleared up. With the return of the mental symptoms, the eczema reappeared.

In 1936 Beauchemin[7] reported 1,000 cases, 100 of epileptics, 200 of manic depressives, 600 of dementia precox, and 100 controls on which allergic studies were made. He got a high percentage of reactions in the epileptics to foods, and in the other cases to tests made with endocrine gland substances. This deserves further investigation.

The students of allergy have scarcely scratched the surface of the relation of protein hypersensitivity to diseases of the nervous system. It is possible that, if psychiatrists and neurologists would keep more in mind this diagnostic and therapeutic aid, other obscure neuropsychiatric problems might be solved.

SUMMARY

1. Allergic reactions consist of local edema, smooth muscle contraction and glandular hypersecretion.

2. If the reaction occurs within the cranial cavity it may produce symptoms simulating brain tumor or cerebral anemia.

3. The result may be headache, vomiting, dizziness, convulsions, transient paralysis and other neurological manifestations.

4. Some cases diagnosed migraine, cyclic vomiting, Ménière's syndrome and epilepsy are really the results of allergic reactions in the central nervous system.

5. If the allergic causes are determined in these cases, prompt cures result.

6. Central nervous system allergic reactions may cause psychic manifestations.

7. Thorough allergic study of cases of periodic psychosis may add to our knowledge of the etiology of such conditions.

8. When patients with recurring psychoses give a family or personal

history of allergic disease, they should be given a thorough investigation of their allergic idiosyncrasies and the appropriate treatment indicated thereby.

SUMARIO

1. Las reacciones alérgicas son compuestas de edema local, contracción del músculo liso y hipersecreción glandulosa.

2. Si la reacción ocurre en la cavidad del cráneo, puede producir síntomas asemejando un tumor o anemia cerebral.

3. El resultado puede ser jaqueca, vómito, vértigo, convulsiones, parálisis transitoria y otras manifestaciones neuróticas o neurológicas.

4. Ciertos casos diagnosticados como jaquecas (migraines), vómito cíclico, sindromo de Ménière y epilepsia son en realidad los resultados de reacciones alérgicas en el sistema nervioso central.

5. Si en estos casos los factores alérgicos son determinados curas inmediatas resultan en ellos.

6. Las reacciones alérgicas del sistema nervioso central pueden causar manifestaciones psíquicas.

7. Por medio del estudio alérgico etiológico sobre las psicoses periódicas podemos llegar a saber la etiología de estas condiciones.

8. Cuando hay enfermos con psicoses periódicas con antecedentes hereditarios y personales alérgicos, se debe investigar en ellos todas sus idiosincrasias alérgicas y también hacer la terapia particular.

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ETIOLOGY OF SEASONAL HAY FEVER IN THE DISTRICT OF COLUMBIA

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THE hay-fever flora vary widely in different parts of the United States. To determine the etiology of seasonal hay fever in any particular locality, a triple approach is indicated; (1) local field observations to ascertain the varieties of anemophilous plants present, their abundance, and pollinating periods; (2) pollen-slide studies to identify and count the pollen grains present in the air from day to day throughout the hay-fever seasons, and (3) skin tests with a large number of different pollen extracts to reveal the allergic sensitivities of the hay fever sufferers residing in that locality. From such studies on plants, pollens, and patients, I learned that nearly all of the seasonal hay fever in the District of Columbia is due to relatively few different pollens. This is fortunate, for according to Hitchcock and Standley[2] there are some 646 genera and 1,630 different species of plants in the District of Columbia and vicinity.

In addition to Hitchcock and Standley's "Flora of the District of Columbia," an article by Bernton, "Dates of Pollination of Anemophilous Plants in the District of Columbia and Vicinity",[1] and a pocket manual "Trees of the District of Columbia" by Mattoon and Alburtis,[3] have been consulted in preparing this article.

TYPES OF SEASONAL HAY FEVER

There are three distinct types of seasonal hay fever in the District of Columbia; namely, early spring, due to tree pollens; late spring and early summer, due to grass and plantain pollens, and the fall variety, which is by far the most common, due to the pollen of the ragweeds. The fall type, as a rule, is of longer duration and greater severity than either spring or summer hay fever. From a careful analysis of the case records of all the seasonal hay-fever patients seen by me during one year, I estimated that in the District of Columbia and vicinity, the early spring type constituted about 4 per cent of the entire group, the late spring and summer cases about 32 per cent, and the fall variety about 64 per cent. Approximately one-fourth of the late spring and summer cases were of the combined summer and fall types, or in other words, about 72 per cent were due to ragweed, either wholly or in part. About 40 per cent of the spring or summer hay-fever victims developed asthma at some time during the course of the disease, whereas of those with fall hay fever, about 50 per cent developed asthma.

EARLY SPRING HAY FEVER

The period from March to June constitutes the early spring or tree hay-fever season in the District of Columbia, although occasional persons develop symptoms as early as the latter part of February.

Poplar.—The poplars *(Populus)*, of which there are eleven different species in the District of Columbia and vicinity, cause some of the hay fever during March and April. In my experience, the northern cottonwood *(Populus virginiana)* and the common cottonwood or Carolina poplar *(Populus deltoides)*, which pollinate in April, are the most important members of this group. The white or silver poplar *(Populus alba)* pollinating in March, the large-toothed aspen or large-tooth poplar *(Populus grandidentata)* pollinating in April, and the Lombardy poplar *(Populus nigra italica)*, are also worthy of mention.

The poplars belong to the *Salicaceae* or willow family. The willows pollinate during March, April, and May. Two of the eleven species of willow trees in this locality are the crack willow *(Salix fragilis)* and the black willow *(Salix nigra)*, both of which pollinate in April and May.

Hickory-Walnut.—The hickory tree *(Hicoria* or *Carya)*, of which there are seven different species in the District of Columbia and vicinity, is responsible for quite a few cases of early spring hay fever. The nutmeg hickory *(Hicoria myristicaeformis)* and the pecan *(Hicoria pecan)* are the most important members of this group. The bitternut hickory *(Hicoria cordiformis)*, mockernut hickory *(Hicoria alba* or *Carya tomentosa)*, pignut hickory *(Hicoria* or *Carya glabra)*, and shagbark or shell-bark hickory *(Hicoria* or *Carya ovata)*, might also be mentioned.

The hickory and pecan trees pollinate during May, and belong to the *Juglandaceae* or walnut family. The black walnut tree *(Juglans nigra)*, which is another member of this same family, accounts for an occasional case of hay fever during April and May. Closely related to the black walnut is the butternut or white walnut *(Juglans cinerea)*, which also pollinates in April and May.

Birch.—The cause of quite a number of cases of early spring hay fever is the birch tree *(Betula)*, of which three different species are encountered in this section, pollinating during April. Red, black or river birch *(Betula nigra)* is the most important variety, and the others are sweet or cherry birch *(Betula lenta)*, also known as black birch, and yellow birch *(Betula lutea)*.

The birches belong to the *Betulaceae* family, of which the blue beech or American hornbeam *(Carpinus caroliniana)* also known as ironwood or water beech, the hop hornbeam or ironwood *(Ostrya virginiana)*, the hazelnut *(Corylus americana)*, and the alder *(Alnus rugo-*

sa), are also members. The hazelnut and alder pollinate the fourth week in February and during March, and the blue beech and hop hornbeam pollinate in April.

Oak.—Oak tree *(Quercus)* pollen, which is shed during April and May, is by far the most frequent cause of early spring hay fever in this section. There are twenty-three different species growing in the District of Columbia and vicinity, but they are all so closely related that to skin-test with an oak pollen mixture or some representative species is sufficient for determining sensitivity. In my experience, white oak *(Quercus alba)*, black oak or quercitron *(Quercus velutina)*, northern red oak *(Quercus borealis maxima* or *Q. rubra)*, scarlet oak *(Quercus coccinea)*, and bur or mossy-cup oak *(Quercus macrocarpa)*, are the five most important varieties with regard to hay fever. Other species that might be mentioned are southern red or Spanish oak *(Quercus rubra* or *digitata)*, willow oak *(Quercus phellos)*, shingle oak *(Quercus imbricaria)*, black jack or jack oak *(Quercus marilandica)*, pin or swamp oak *(Quercus palustris)*, post oak *(Quercus stellata* or *minor)*, swamp white oak *(Quercus bicolor* or *platanoides)*, rock chestnut oak *(Quercus montana* or *prinus)*, basket or swamp chestnut oak *(Quercus prinus* or *michauxii)*, and chestnut oak or chinquapin oak *(Quercus muhlenbergii)*. Oak leaves differ from those of other trees in that they are rather thick, shiny, and usually deeply serrated.

The oaks belong to the *Fagaceae* or beech family, and other members of this same family are the beech or beechnut tree *(Fagus grandifolia* or *americana)*, which also pollinates in April and May; and the chestnut *(Castanea dentata)*, and the chinquapin *(Castanea pumila)*, both pollinating in June.

Elm.—The pollen of the elms *(Ulmus)*, of which there are three different species in the District of Columbia, causes some people to have hay fever during March. The two most important species are the red elm *(Ulmus fulva)*, which is also known as the slippery elm, and the American, white or water elm *(Ulmus americana)*. The pollen of the red elm has an unusually pungent odor, smelling like the old-fashioned slippery elm cough lozenges. The third species of elm found in the District is the English elm *(Ulmus campestris)*.

The elms belong to the *Ulmaceae* family, of which the hackberry or sugarberry *(Celtis occidentalis)* is also a member. The hackberry pollinates in May.

Mulberry.—The paper mulberry tree *(Papyrius* or *Broussonetia papyrifera)*, which pollinates during May, is another fairly important cause of early spring hay fever and asthma in the District. The paper mulberry catapults its pollen into the air by a spring-like action of the

stamens, so that during pollination the tree appears to emit tiny puffs of smoke. The trees are nearly all males, and are propagated from sprouts.

Other members of the mulberry *(Moraceae)* family, such as the red mulberry *(Morus rubra)* or the white mulberry *(Morus alba)*, pollinating at the same time as the paper mulberry, may be important contributing factors in this type of hay fever. Osage orange or mock orange *(Toxylon pomiferum)* is another member of the mulberry family, also pollinating in May.

Sycamore.—The American sycamore *(Platanus occidentalis)* of the *Platanaceae* or plane-tree family, is one of the more important hay-fever trees in this section. The sycamore, also called buttonwood or buttonball tree, pollinates during the latter part of April and in May. The balls of the native sycamore are solitary, while the London plane *(Platanus acerifolia)* and the oriental plane *(Platanus orientalis)* trees commonly have two or more balls on a single, pendant stem.

Maple.—Responsibility for some cases of early spring hay fever rests with the maples *(Acer)*, of which seven different species are found in the District of Columbia and vicinity, pollinating anywhere from January to May. The maples are not catkin-bearing trees, and are polygamous or dioecious. The most important species are the red or scarlet maple *(Acer rubrum)* also called swamp maple, which pollinates from February to April, and the Norway maple *(Acer platanoides)*, which begins to shed pollen about the second week of April. Among other locations in Washington, 16th Street, N. W. (Avenue of the Presidents) from H Street north to the District Line (Alaska Avenue), is planted with Norway maples, including over 500 memorial trees marked with the names of those from the District of Columbia who gave their lives in the first World War.

The sugar or hard maple *(Acer saccharum)* and the silver or soft maple *(Acer saccharinum)* might also be mentioned. The silver maple pollinates anywhere from January to March, being one of the earliest trees to flower in the spring, and the sugar maple pollinates in May.

The pollen of the boxelder or ash-leaved maple *(Rulac* or *Acer negundo)*, which is another member of the *Aceraceae* or maple family, is also the specific cause of an occasional case of hay fever. The boxelder sheds its pollen during April.

Ash.—The ash trees *(Fraxinus)*, of which there are six different species in the District of Columbia and vicinity, are to blame for an occasional case of hay fever during April and May. Of this group, water ash *(Fraxinus caroliniana)* and white ash *(Fraxinus americana)* have been the most potent reactors in my experience. Black ash *(Fraxinus nigra)*, red ash *(Fraxinus pennsylvanica)*, and green ash *(Frax-*

inus pennsylvanica lanceolata), are also worthy of mention. Green ash pollinates in May, and the other species referred to, in April and May. Although all of the ashes are dioecious, black ash is also polygamous, and white ash is rarely monoecious or polygamous.

The ash trees belong to the *Oleaceae* or olive family, of which the common lilac *(Syringa vulgaris)* is also a member.

Cedar.—Eastern red cedar *(Juniperus virginiana)* pollen is an infrequent cause of early spring (February or March) hay fever in the District of Columbia. Sensitization to red cedar is almost invariably associated with sensitization to mountain cedar *(Juniperus sabinoides)* from former residence in Texas where the mountain cedar is so prevalent.

The junipers belong to the pine family *(Pinaceae)* as do scrub or Virginia pine *(Pinus virginiana)*, white pine *(Pinus strobus)*, pitch pine *(Pinus rigida)*, loblolly or old field pine *(Pinus taeda)*, yellow or shortleaf pine *(Pinus echinata)*, and four other species of pine trees in this locality. The scrub pine is found in great abundance throughout the District, and pollinates during April and May.

Another member of the *Pinaceae* that might be mentioned is eastern hemlock *(Tsuga canadensis)*.

Although I have mentioned the most important producers of early spring hay fever in the District of Columbia, any other variety of wind-pollinated tree, such as the maidenhair tree *(Ginkgo biloba)*, the sweet or red gum *(Liquidambar styraciflua)*, and the honey locust *(Gleditsia triacanthos)*, may be the causative agent in individual instances. The ginkgo sheds its pollen in April, the sweet gum during the last two weeks of April and in May, and the honey locust in May.

Flowers of honey locust are fragrant and nectar-laden. The honey locust belongs to the *Caesalpiniaceae* or senna family, whereas the black locust, to be referred to shortly, is a member of the *Fabaceae* or pea family.

Some trees such as the black or sour gum *(Nyssa sylvatica)* also called tupelo, and the tree of heaven *(Ailanthus altissima* or *glandulosa)* are wind pollinated as well as insect pollinated, and hence are potential causes of hay fever. The black gum pollinates in May, and the tree of heaven from the third week of May to July.

Although the basswood or American linden *(Tilia americana)* and the swamp magnolia or sweet bay *(Magnolia virginiana)* are insect-pollinated trees, they produce a large amount of pollen during May and June, some of which gets into the air.

The black or yellow locust *(Robinia pseudo-acacia)* pollinating in May, sassafras *(Sassafras variifolium* or *officinale* or *sassafras)* which flowers about the middle of April, hop tree or wafer ash *(Ptelea trifoliata)* pollinating in May and June, horse chestnut *(Aesculus hippocastanum)*, per-

simmon *(Diospyros virginiana)* which flowers in May, and American holly *(Ilex opaca)* pollinating in May and June, produce a moderate amount of insect-borne pollen, and would be capable of causing hay fever only on intimate exposure. Holly flowers are usually dioecious and often polygamous.

The tulip tree or yellow poplar or white wood *(Liriodendron tulipifera)* May-June, papaw *(Asimina triloba)* April-May, witch hazel *(Hamamelis virginiana)* autumn, shadbush or serviceberry or Juneberry *(Amelanchier canadensis)* April, redbud or Judas tree *(Cercis canadensis)* April, flowering dogwood *(Cornus florida)* April-May, mountain laurel *(Kalmia latifolia)* May-June, elder *(Sambucus canadensis)* May-July, wild black cherry *(Prunus serotina)* May, choke cherry *(Prunus virginiana)* May, wild plum *(Prunus americana)* April, and Japanese flowering cherry *(Prunus pseudocerasus* or *yedoensis)* late March or early April, are all insect-pollinated and of no importance in the hay-fever problem.

The largest collection of Yoshino cherry trees *(Prunus yedoensis)* outside of Japan, surrounds the Tidal Basin in Potomac Park, Washington, D. C. The beauty of their blossoms attracted a great influx of visitors to the Nation's Capital every spring, prior to the war with Japan.

Before leaving the subject of early spring hay fever, I should like to call attention to the fact that because of the many thousands of trees lining our city streets and decorating our parks, it is not necessary to go into the woods to contact large quantities of tree pollen. Washington today has 126,000 street trees, which is more than any other city in the world.

LATE SPRING AND EARLY SUMMER HAY FEVER

The late spring and early summer hay-fever season in the District of Columbia is from about the tenth or middle of May until the fourth or middle of July, or occasionally the first of August. It is commonly spoken of as "rose cold" or "rose fever," but these are misnomers, as roses are rarely ever the cause. Only wind-pollinated plants can be held responsible for hay fever. Clover, daisies, dandelions, honeysuckle, roses, and all other brightly colored flowers with sweet odors, are insect-pollinated. If a person should happen to be sensitive to rose pollen, which is unusual, symptoms of hay fever could be produced only by intimate exposure to roses, and even then the effect would be more or less transitory.

Common dandelion *(Leontodon taraxacum* or *Taraxacum officinale)*, although very abundant in waste ground, open fields, and lawns, is insect-pollinated and can cause hay fever only on direct inhalation, such as by children picking and smelling the blooms. It pollinates from April to June, but the familiar yellow flowers may be found at nearly any time of year, even in midwinter if there are a few warm days. Dandelion is botanically related to ragweed, being a member of the *Cichoriaceae* or chicory family.

Grass.—From testing a large number of hay-fever patients routinely with many different pollens, I learned that nearly all (about five-sixths) of the late spring and early summer hay-fever patients from the District of Columbia and vicinity were definitely sensitive, though in varying degrees, to the pollens of the following six grasses: sweet vernal *(Anthoxanthum odoratum)*, June or Kentucky blue grass *(Poa pratensis)*, orchard *(Dactylis glomerata)*, perennial rye *(Lolium perenne)*, redtop *(Agrostis palustris* or *alba)*, and timothy *(phleum pratense)*.

Plantain.—A relatively small number (about one-sixth) of the late spring and early summer hay-fever patients from the District of Columbia reacted to the pollen of English plantain *(Plantago lanceolata)* also known as rib grass, and a few (about one-tenth) reacted to both plantain and grasses.

Plantain belongs to the *Plantaginaceæ* family. There are seven different species in the District of Columbia and vicinity, including common plantain *(Plantago major)*, which pollinates from June to September, although I have known only English plantain to cause hay fever. English plantain is not a grass, nor does it have any botanical relationship to the grasses, but merely pollinates at the same time.

The six grasses, previously referred to, pollinate successively in the District in the order named, sweet vernal commencing the second week in May, Kentucky bluegrass the third week in May, orchard the third or fourth week in May, perennial rye the last week in May or the first week in June, redtop the first or second week in June, and timothy the second week in June. English plantain begins to pollinate about the same time as the grasses, namely, the second week in May, and continues until about the first of August. In other words, sweet vernal and orchard bloom in May, bluegrass in May and the first week of June; perennial rye in June; redtop and timothy in June and July; and plantain pollinates from May to August. Thus the period of pollination of the six grasses and English plantain coincides exactly with the late spring and early summer hay-fever season in the District of Columbia. Furthermore, these grasses and plantain, which are all native to Europe and naturalized in the United States, grow in great abundance in this locality, and are wind-pollinated. Their pollen grains, being light and dry, are floating around in the air in large numbers, and under favorable conditions are carried long distances by the wind.

Very sensitive grass hay-fever patients may occasionally develop symptoms as early as the latter part of April, due to annual bluegrass *(Poa annua)* which pollinates at that time, or may even bloom in warm weather during the winter.

Other members of the grass family that might be mentioned are velvet grass *(Notholcus* or *Holcus lanatus)*, couch grass *(Agropyron repens)*, meadow fescue *(Festuca elatior)*, Johnson grass *(Holcus* or *Andropogon*

halepensis), yellow foxtail *(Chaetochloa lutescens)*, wild rice *(Zizania palustris)* which is also called Indian rice or water rice, barnyard grass or cockspur *(Echinochloa crusgalli)*, and crabgrass *(Syntherisma sanguinalis)*. Velvet grass pollinates in June, couch grass and meadow fescue pollinate in June and July, Johnson grass pollinates during July and August, yellow foxtail, wild rice and barnyard grass all pollinate from July to September, and crab grass from July until frost.

Some Bermuda grass *(Capriola* or *Cynodon dactylon)* is present in the District of Columbia, pollinating in the summer beginning the first week of July, but there is not enough of this grass to be of clinical importance.

The grass family *(Poaceae)* in the District of Columbia and vicinity consists of eleven tribes, fifty-seven genera, and 186 different species. Also belonging to the grass family are corn or maize *(Zea mays)*, rye *(Secale cereale)*, and the other cereal grains, with the exception of buckwheat. Corn pollinates in July and August, and rye during May and June.

Dock.—A rare cause of summer hay fever in this locality is sheep sorrel *(Rumex acetosella)*, which pollinates from the second week in May until the third week of July. Sheep sorrel belongs to the docks *(Rumex)*, as does narrow or curly or yellow dock *(Rumex crispus)*, which pollinates from the third week in May through July. The docks, of which there are six different species in the District of Columbia, are members of the *Polygonaceae* or buckwheat family.

Chenopod.—Lamb's-quarters or pigweed *(Chenopodium album)* pollinates in the District of Columbia anywhere from June to October, but is an extremely rare cause of hay fever in this locality.

Lamb's-quarters belongs to the *Chenopodiaceae* or goosefoot family, as does wormseed *(Chenopodium ambrosioides)*, which pollinates from July to October.

Russion thistle or saltwort *(Salsola pestifer* or *kali)*, another member of the goosefoot family, pollinating from July to September, has been reported from this locality, but is too scarce here to be of any importance.

I might also mention three members of the neighboring *Amaranthaceae* or amaranth family, namely, spiny amaranth *(Amaranthus spinosus)*, tumbleweed pigweed *(Amaranthus graecizans)*, and redroot pigweed *(Amaranthus retroflexus)*, all pollinating from July to October.

There is some hemp *(Cannabis sativa)* in the District of Columbia and vicinity, pollinating from June to August. Hemp is a member of the *Urticaceae* or nettle family.

FALL HAY FEVER

Ragweed.—The autumnal hay-fever season in the District of Columbia is from the middle of August until the arrival of frost. This time corresponds to the period of pollination of ragweed *(Ambrosia)*, which is the

cause of practically all of these cases. There are two varieties of ragweed in this section; namely, the common or short ragweed *(Ambrosia elatior* or *artemisiaefolia)*, and the giant or high ragweed *(Ambrosia trifida)*. Giant ragweed pollinates from the second week in August until the third week of September, and short ragweed pollinates from the third week in August until frost, which usually occurs in the first part of October.

Very occasionally a patient will react to short ragweed and not to giant, and more rarely one will be found to react to giant and not to short; but almost all of the fall hay-fever victims react to both varieties.

Short ragweed is a dirty green weed that grows abundantly on vacant lots, waste ground, and along roadsides. It thrives best in soil that has been cultivated and then neglected. Short or low ragweed varies from a few inches to from 3 to 5 feet in height. The leaves branch and rebranch, resembling those of some species of wormwood or *Artemisia;* this form of ragweed is known, therefore, as *Ambrosia artemisiaefolia.*

Giant or great ragweed, also spoken of as horseweed, grows best in moist soil near streams and along river banks, and ranges in height from 5 or 6 to even 10 or 12 feet. The leaves of this variety are distinctive in that they are always three-nerved and usually three-lobed, accounting for the botanical term *"Ambrosia trifida,"* although leaves may be five-lobed or not divided at all.

Cocklebur.—Some of the fall hay-fever patients in the District of Columbia are sufficiently sensitive to another member of the *Ambrosiaceae* or ragweed family, namely, cocklebur *(Xanthium)*, to justify inclusion in their treatment. Cocklebur pollinates from August to October, and there are three different species in this locality, namely, spiny cocklebur or clotbur *(Xanthium spinosum)*, American cocklebur *(Xanthium americanum* or *canadense)*, and common cocklebur *(Xanthium commune* or *saccharatum)*.

Wormwood.—Other fall hay-fever patients in the District of Columbia react sufficiently to mugwort or wormwood *(Artemisia vulgaris)*, and annual sage or annual wormwood *(Artemisia annua)*, to warrant treating with one or both in addition to ragweed.

Mugwort does not begin pollinating until about the second week in September, and annual sage pollinates in August and September. The wormwoods belong to the *Asteraceae* or aster family.

Goldenrod.—Goldenrod *(Solidago)*, of which there are twenty-one different species blooming in the District of Columbia and vicinity from July until October, has been erroneously held to be the cause of fall hay fever. Although conspicuous in the fields, goldenrod produces very little pollen, which is difficult to dislodge from the plant. Smelling goldenrod may cause sneezing, but this is usually due to ragweed pollen clinging to the goldenrod.

Goldenrod is another member of the large *Asteraceae* family, as is the common sunflower *(Helianthus annuus)* blooming in July and August, but being insect pollinated, can cause symptoms only on intimate exposure in very sensitive persons.

Other common insect-pollinated members of the aster family that bloom in the fall are aster, cosmos, dahlia, and golden glow.

Cichoriaceae, Ambrosiaceae, and *Asteraceae* are often united as *Compositae,* which family is characterized by an inflorescence conspicuously different from other plants, in that what appears to be a single flower is a composite aggregation of a large number of individual flowers.

In closing this article, I would again emphasize that the only pollens which commonly produce hay-fever symptoms of any duration are those that are floating around in the air, and can be breathed in with normal respiration.

SUMARIO

La flora de la fiebre de heno (polinosis) varía mucho en las diversas partes de los Estados Unidos. Para determinar la etiología de la fiebre de heno estacional en cualquiera localidad particular, es necesario hacer estas tres cosas: (1) la observación o el exámen del campo para confirmar las variedades de plantas anemófilas presentes, su abundanica, y los períodos de polenización; (2) los estudios del polen con un portaobjeto para identificar y hacer la cuenta de los granitos de polen presentes en el aire de día en día, durante toda la estación de la fiebre de heno: y (3) las pruebas cutáneas con un gran número de varios extractos de polen para descubrir las sensibilidades alérgicas en los residentes de equalla localidad que sufren de fibre de heno. De tales estudios sobre plantas, polenes, y enfermos, he aprendido que casi toda la fiebre de heno estacional en el distrito de Columbia es debida relativamente a pocos diferentes pólenes. Esto es bienes de fortuna, porque según Hitchcock y Stanley hay unos 646 generos y 1630 diferentes especies de plantas en el dístrito de Columbia y vecinidad.

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THE PRESENCE OF THERMOSTABLE INHIBITING FACTOR IN THE SERA OF PATIENTS TREATED FOR HAY FEVER BY INJECTIONS OF POLLEN EXTRACT

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THE principle of desensitization as a treatment for pollinosis was a natural sequel to the observations of Wolff-Eisner[27] and Meltzer[22] that hypersensitivity of human beings might be analagous to anaphylaxis in animals. It is a characteristic of anaphylactic phenomena that a sensitized animal becomes "refractory" immediately following an injection of a subliminal dose of his antigen. Besredka[1] protected guinea pigs, experimentally sensitized to horse serum, by a single injection which was 200 times below the postulated lethal dose. One injection of this type enabled the guinea pig to tolerate without reaction several times the lethal dose. Many other workers, including Otto[23] have observed this phenomenon. It was assumed in explanation, that anaphylactic shock was a reaction between antigen and antibody, and that the protection from anaphylactic shock conferred by an injection of a sublethal dose of antigen was due to the antigen sufficiently exhausting the antibodies so that further antigen could only produce a minimal rather than a violent reaction. Dale[12] supported this hypothesis with his demonstration that the uterine segment of a guinea pig which had first been sensitized to horse serum and then desensitized, would not contract when more antigen was added to the bath, presumably because the tissue antibodies had been exhausted by the desensitizing effect of the original antigen.

This concept of literal desentization, or qualitative decrease in the patient's anaphylactic antibodies was held by many clinicians as explaining their results in their treated patients. In 1917, Coca[5] stated: "The mechanism of the alleviating effect of specific therapy is the same as that of desentization in experimental anaphylaxis."

In 1926, Kolmer[15] said: "I believe that the specific treatment of hay fever and bronchial asthma by the subcutaneous injections of extract of the inciting agent or agents is a process of true desentization by which the anaphylactic antibodies in the sensitized cells are exhausted." Phillips[24] in 1926 remarked (after reporting a diminution in the size of skin tests after injections of pollen extract), desensitization "must be obtained in every case no matter how many doses are required, nor how large." In 1931, Brown[2] stated, "If the treatments are given over a long enough period of time, and sufficiently strong doses are used, most

The expenses for this work were defrayed by the Asthma Research Foundation, Inc., Boston, Mass.

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patients will show a marked reduction in skin reactions, and a number will show complete disappearance." There were many reports which, while not totally consistent, tended to support this concept that the patients under specific protein injection treatment were literally desensitized. Their support lay in their demonstrating a quantitative decrease in serum and tissue reagins as measured by skin or ophthalmic tests, implying that the patient's response to antigen is curtailed because his antibodies have become exhausted or saturated by the administered antigen.

However, the concept that treatment by pollen extract injections really desensitizes the patient literally, as anaphylactic shock appeared to desensitize animals that recover, was soon questioned. Weil[26] had found that diminished susceptibility to anaphylactic shock occurred when a quinea pig was injected repeatedly at short intervals with a foreign protein, although at the same time the specific sensitizing antibody titer of the animal's blood rose, as measured by the increased capacity of its serum to sensitize a normal guinea pig.

Weil postulated that his sensitized animals were refractory to anaphylactic shock because the increased free antibodies circulating in the blood combined with the free antigen, and prevented free antigen from reaching tissue cells where the interaction might produce anaphylactic shock. Manwaring and Kusanna[20] supported Weil when they removed the uterus from a guinea pig "immunized in the same manner, washed it free of all circulating antibodies, and found that the organ reacted to the specific antigen in the same manner as did a uterus from a highly sensitized guinea pig.

When Coca and Levine,[7] in 1926, reported that in many of their patients treatment definitely increased the reagin contents of their sera, it seemed that Weil's concept might be applied to human beings, and that the mechanism of protection in the treated allergic patient might be a neutralization of antigen by increased circulating reagins which protected or buffered the tissue cells. Many other reports by Markow,[21] Cooke,[8,9] Caulfield[3] and Rackemann[25] tended, though inconsistently, to support Levine. Markow and Spain went so far as to suggest that in cases reported where skin tests appeared to be reduced by treatment the apparent reduction was due entirely to deterioration of the pollen extracts used for testing. The application of this concept to patients seemed especially logical after Levine and Coca[17] reported that reagin-antigen mixtures reacted when injected into atopic human skin.

It would appear that the physiologic mechanism by which allergic manifestations are controlled in treated patients may differ according to individual patients and the exact technique of treatment. Some patients when treated by injections of pollen extracts may be partially (and literally) desensitized, other patients may obtain their clinical relief from an increase of circulating reagins which may act as a brake on the supply of antigen reaching the sensitized tissue cells. However, a large group of

patients, perhaps 20 per cent, do not show any marked change in reagin concentrations after injection treatment, and in this group it would seem that the clinical immunity must be related to some other factor.

Cooke,[10] in 1935, first suggested that the tolerance which patients acquire by treatment with pollen extracts was due to an active development of immune antibodies, antibodies which were different and separate from those associated with skin sensitization. He stated that the blood of actively-treated ragweed cases, when transferred into non-treated patients gave relief of acute hay fever symptoms in sixteen out of twenty cases, indicating that active treatment had produced in the blood of treated patients a transferable protective substance. He also demonstrated that when serum from a treated ragweed patient was mixed with ragweed and injected into normal skin, no raction, or a definitely diminished reaction occurred. These experiments led him to believe that extract-injection treatment produced an antibody which prevented the reaction between allergen and reagin. However, Cooke did not observe any definite inactivation of antigen by the inhibiting antibody when mixtures of the two were tested in naturally sensitive skins, so he was led to conclude, erroneously, that the inhibitory antibody did not bind its antigen. The presence of this inhibitory antibody was confirmed by Harley[14]

In 1937, Cooke[11] and others, showed that in non-sensitive patients evidence of active immunity to pollen substances could be engendered by the injections of the specific extract, and in 1938, Cohen[4] was able to produce, by repeated injections of pollen extract, immune antibodies in normal sheep.

Loveless, [18,19] in 1939, demonstrated for the first time and conclusively that injections of pollen extract produced in the serum of treated patients, an antibody which would combine with and inactivate its homologous antigen. This antibody definitely differs from reagin in that it is non-sensitizing, and is thermostable. We have attempted in this work to confirm the experiment of Loveless.

The rationale of the technique rests on that fact that the quantity of immune antibody developed in the serum of a treated allergic patient can be estimated by two procedures. First, one can estimate the capacity of that serum to inhibit the reaction which would naturally occur when a passively sensitized site is tested with free antigen. If the antigen is completely bound no reaction will occur; in these sites in which reactions do occur, the degree of response will be proportional to the amount of immune antibody present. Second, one can re-inject these same sites with an excess of antigen. It is obvious that in those sites in which the antigen first injected was bound and inactivated completely, the amount of reagin is still present in the original quantity, and an injection of an excessive amount of antigen will produce a maximum reaction; while in those sites in which the antigen first injected was not completely inactivated, so that some of the reagin and antigen combined, there will be a

diminished amount of reagin present, and the injection of an excessive amount of antigen will produce a relatively smaller reaction.

In order to carry out a quantitative study, all sites to be compared must be passively sensitized with the same quantities of reagins. This can be accomplished by passively sensitizing each site with the same amount of the same ante-treatment serum. To keep the reagin content of all the sites equal when post-treatment serum is added, reagins in the post-treatment serum must be destroyed. Destruction of the reagins in the post-treatment sera is accomplished by heating, in such a manner as to leave the immune bodies unimpaired:

The actual technique can be outlined:

1. "A" (ante-treatment) serum is collected before the treatment of the patient's ragweed sensitivity is begun. The serum is obtained at least six days after the skin tests, since Feinberg[13] has shown that antigen injected subcutaneously may remain *in situ* for at least forty-eight hours. The serum is then stored in the icebox. Wassermann reactions and bacterial cultures are done in order to insure sterility. No experiments are done during the pollen season.

2. "P" (post-treatment) serum specimens are collected ideally when the patient has reached those stages of his treatment at which he is receiving at each treatment, 1,000 P.N.U., 5,000 P.N.U., and 10,000 P.N.U. of ragweed extract. Blood is taken two weeks following the last injection.

3. "P" serum is heated for one hour at 60 C. in a constant temperature bath. From our work, as well as Loveless', Coca's, and that of others, it has been shown that all demonstrable skin-sensitizing reagins are destroyed by this procedure.

4. Vials are set up in series. With chemically clean, sterile .25 ml. pipettes, one series of vials is instilled with mixtures of constant amounts of autogenous serum "A" and progressive dilutions of the ragweed extract; another series with mixtures of constant amounts of autogenous serum "A," heated serum "P," and the progressive dilutions of ragweed extract. Saline is added to the first series to keep the volume relationships constant in all testing mixtures. The "A" serum added to the heated serum in the second series is, in almost every instance, the patient's own "A" serum. In a few of our cases it consisted of pooled "A" sera of known reaginic activity. Two volumes of buffered saline is added to the serum used in the control mixture. After the ingredients are mixed, the vials are allowed to stand one hour.

5. Using the skin of the back of a test subject, known by history and skin tests to be non-atopic, 0.1 ml. from each vial is injected for a series of test cites. These sites are .3 inches apart and do not come within 2 inches of the spine. A graduated 1 ml. tuberculin syringe is considered sufficiently accurate for performing these injections. Test subjects are not used more than once in three months; however, with the excess of antigen that is used, there is no possibility that reagins will remain in any of the passively sensitized sites.

6. The reactions are read in fifteen to thirty minutes. Within that period of time the plain serum controls are practically negative. In quite a few instances, however, the non-specific irritation does not subside before the specific reactions reach their maximum, which unfortunately renders the interpretations of the reactions difficult. In fact, serum irritation is so common that it seems preferable to depend, as a rule, on the retest endpoints.

7. After twelve to eighteen hours, when all or practically all signs of the first test had disappeared, each test site is re-injected with .025 ml. of a dilution of ragweed extract containing 10,000 P.N.U. per ml. For these injections a ¼ ml. tuberculin syringe is used, attempting to insert the needle into the same puncture

TABLE I. TYPICAL TITRATION REACTIONS OF SERUM TAKEN BEFORE AND AFTER TREATMENT

Maximum Injection Dose: Ragweed: 5000 Protein Nitrogen Units
Titer of Immune Bodies in "A" Serum: 10-25 Protein Nitrogen Units
Titer of Immune Bodies in "A" Serum and Heated "P" Serum: 250-500 P.N.U.

Antigen (P.N.U.) Original Site.	Initial Tests		Final Tests (12 Hours)	
	"A" Serum	"A" Serum and Heated "P" Serum	"A" Serum	"A" Serum and Heated "P" Serum
10				
25				
50				
100				
250				
500				
1000				
1500				
Control				

orifice produced by the injection of the sensitizing injection. It is assumed that this volume is sufficiently great to be distributed to all parts of the sensitized site. Comparison with the results of Loveless indicates that our retest endpoints are somewhat higher because we used ragweed antigen of 10,000 P.N.U. instead of 1,000 P.N.U. in these retests. This was to be expected.

The reactions are observed at 10, 20, 30, and 40-minute intervals. When the non-specific reactions appear minimal and the specific reactions, maximal, the sites are graded as 1, 2, 3, or 4 plus. They are then traced and photographed. The titer of a given unheated serum or a mixture of this serum with a heated

TABLE II. TITRATIONS OF IMMUNE ANTIBODY

Patient	P.N. Units of Antigen Required to Neutralize 1 ml of "A" Serum	P.N. Units Required for Neutralization of 1 ml of "A" Serum and 1 ml of Heated "P" Serum	P.N. Units of Antigen Given Patient by Injection as Maximum Dose
P.S.	10	100	1,000
P.S.	10	250	5,000
C.B.	50	1,000	4,500
M.H.	10	250	3,000
A.M.	10	50	1,000
D.S.	10	250	1,000
P.W.	10	50	1,000
P.W.	10	1,500	1,000
D.L.	10	50	1,000
E.J.	10	100	800
R.M.	10	100	2,000
E.S.	10	25	200
H.N.	10	1,500	2,000
M.C.	10	50	900
M.C.	10	25	3,000

serum is expressed as the number of units of antigen originally present in that site which on subsequent testing gave a plus-minus reaction. The last positive reaction, or plus-minus reaction, is taken for the endpoint. This is done in order to avoid running into the situation of taking as an endpoint that negative reading which might be far past the first negative response attainable.

Results for a typical patient can be seen in the accompanying tracing (Table I), and the results of our total series are shown in Table II.

CONCLUSION

The present investigation confirmed conclusively the demonstration by Loveless of the presence of a thermostable neutralizing factor in the sera of ragweed sensitive hay fever patients. Since this antibody apparently binds antigen, a passively sensitized site in which it is present requires a definite measured additional amount of antigen for neutralization.

CONCLUSION

La investigación presente confirma concluyentemente la demonstración hecha por Loveless de la presencia de un factor neutralizante y termoestable en los sueros de los enfermos hipersensitivos a la fiebre de heno o polinosis por las malezas o ambrosias. Puesto que este anticuerpo según las apariencias ata el antígeno, un sitio pasivamente sensibilizado en que

(Continued on Page 229)

SYMPATHECTOMY AS AN AID IN THE RELIEF OF FAMILIAL NONREAGINIC FOOD ALLERGY

Preliminary Report

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SYMPATHECTOMY has been used most often for the purpose of combating circulatory hypertension, and its use in this condition has been empirical. It is true that the therapeutic success of the operation in many of the subjects with hypertension has led some to believe that this disease was due to some local abnormality of the sympathetic nervous system which was corrected only by sympathetic denervation of the kidneys. Nevertheless, the complete failure of the operation in many other cases has thrown doubt upon this concept and has caused some operators even to deny the conclusion so brilliantly supported by Goldblatt's experiments, that hypertension is essentially a disease of renal origin.

An explanation of these discordant results is found in a recent preliminary report[2] on the etiology of essential hypertension. All of the seven cases forming the clinical material of that report were subjects with nonreaginic food allergy, and in all of them the hypertension was reduced *pari passu* with the relief of the allergy, as judged by the lowering of the pulse rate and the disappearance of the other allergic symptoms (headache, physical tiredness, et cetera). When the allergenic foods were returned to the diet the blood pressure again increased—sometimes to its earlier maximum—diminishing again after elimination of the culprit foods.

It was tentatively assumed, on the basis of the Goldblatt experiment, that in persons with essential hypertension the kidney is a shock organ of food allergy and that the edema that is the characteristic lesion of the local allergic reaction causes an increased pressure within the kidney, which, in turn, compresses the blood vessels and thus impedes the flow of the blood through the organ.

It was also pointed out that in those cases of hypertension in which the slowing of the circulation is due to a narrowing of the vascular channels by infection (glomerulo-nephritis) or arteriosclerosis, the correction of an existing food allergy could not be expected to influence such an irreversible lesion.

It seemed reasonable to suspect that the therapeutic result of sympathectomy could sometimes depend on which of these two conditions obtains in the particular case and this assumption is consistent with the negative results of the operation[4] in dogs in which artificial hypertension has been established with the mechanical method of Goldblatt. These negative results obviously prove that sympathectomy does not influence the physiological *effects* of renal ischemia; hence it would seem reasonable to assume

From the Lederle Laboratories, Pearl River, N. Y.

that if the operation does relieve hypertension it probably does so through some influence upon the cause of the renal ischemia in that individual.

Now, the cause of the renal ischemia in human essential hypertension, as has already been stated above, is assumed to be an intracapsular food-allergic edema; hence the immediate effect of sympathectomy in the relief of such a case must be assumed to be some interference in the food-allergic reaction.

This conclusion has considerable support in several of the reports upon the results of sympathectomy in the treatment of hypertension.

Thus, Rowntree and Adson[8] in their report, eighteen years ago, of a case of malignant hypertension in which sympathectomy failed to affect the elevated pressure, observed:

"Headache and epigastric distress disappeared. Vision improved markedly; blind spots decreased materially."

Then, Crile,[3] in his early report of the results of celiectomy in twenty-eight cases of essential hypertension, wrote:

"In every case, symptomatic relief has been experienced; headache, palpitation, nervousness, et cetera, disappearing while the patients were still in the hospital."

Adson, Craig and Brown[1] state:

"Improvement in clinical symptoms is probably more manifest than the actual drop in blood pressure since these patients very promptly inform us that their throbbing headache, cardiac consciousness and precordial distress disappear."

Smithwick[9] writes:

"We judge the results on the basis of actual fall in blood-pressure level, and also on the basis of symptomatic relief. The latter is so striking and lasting, even in the absence of material blood-pressure change, that we are inclined to feel that *the improvement is the result of this type of operation rather than of temporary blood-pressure changes following nonspecific operative procedure.*" (Italics ours.)

Peet, Woods and Braden[7] comment:

"Many of the patients had blood pressures unchanged by the operation. To them, however, the relief of symptoms, usually headache, was of vital importance. The answer to this apparent paradox is not available at present. Research is being carried on by one of us (W. W. W.) relative to the physiology of cerebrospinal fluid pressure relationships in an attempt to explain *why, following operation, so many patients receive persistent symptomatic relief from their headaches even though their blood pressure continues unchanged or goes even higher.* (Italics ours.)

As Smithwick remarks, the symptoms that were relieved by the sympathectomy were not due to the hypertension because they sometimes disappeared even though the high blood pressure persisted (as was noted also by Peet et al.). Those symptoms, especially headache, have since been shown[2] to be food-allergic.

Through the foregoing analysis, we arrived at the tentative conclusion that in the great majority of instances in which sympathectomy has relieved any human symptom, that effect was accomplished by some interference with the food-allergic reaction, wherever that reaction was located.

As soon as this conclusion was reached it was decided to apply that operation in the relief of the more serious symptomatic manifestations of familial nonreaginic food allergy; especially in those subjects who cannot easily avoid all the excitants of their allergy (inhalants), those whose symptoms may have serious consequences (epileptic seizures and others), and those whose list of nonallergenic foods is too small to support an actively functioning person.

CASE REPORTS

Case 1.—A. F. C., aged sixty-seven. Food-allergic symptoms: migraine, gastric pain, gastro-intestinal bleeding, severe dizziness, recurrent temporary loss of memory, chronic rhinitis, constipation, hemorrhoidal bleeding, colitis, conjunctivitis and others.

The food-allergic history of this patient is described in detail elsewhere.[2] The above-mentioned symptoms had been partially controlled by avoidance of the major food allergens and by numerous injections each day of histamine diphosphate (0.1 mg. of the base at each injection). There had never been a hypertension of serious degree but tests just previous to the operation, with one of the minor food allergens (potato), had revealed a latent tendency to hypertension which was believed to have been restrained by strict avoidance of the major allergens. All but one of the above-mentioned symptoms had also been experienced earlier in his life when the blood pressure had been normal (systolic pressure 108 to 112) and when his diet had been almost entirely unrestricted.

Operation.—Dr. Miscall performed the first stage of the Crile sympathectomy on May 5, 1942; since he is now with the armed forces and unavailable, I must depend upon my recollection of his verbal description of it. Three right lumbar ganglia and the right half of the celiac ganglion were removed retroperitoneally and 2.0 c.c. of absolute alcohol were injected into the left half of the celiac ganglion. On August 18, 1942, three left lumbar ganglia and the left half of the celiac ganglion were removed. Both operations were done under general anesthesia administered by Dr. E. A. Rovenstine.

From the day of the first operation the patient's diet was wholly unrestricted.

On the fourteenth day after the operation, on an unrestricted diet, the blood pressure was 132/72; on the nineteenth day, 120/74; at one month, 114/68; at about two months 158/84; three weeks later 132/78.

There was frequent heartburn from about one month after the operation, growing less marked after the second month. There were also occasional neuralgic episodes affecting the right sciatic nerve and the left occipital region. All of the other allergic symptoms mentioned above have been entirely absent since the operation.

In the third month the neuralgic symptoms increased steadily and on August 18 a left lumbar sympathectomy was performed at the patient's request. There was no noticeable amelioration of the neuralgic symptoms after this second operation. Later, other allergic symptoms (canker sores, moderate heartburn, mild conjunctivitis) appeared from time to time and after eight months slight plantar cramp. *All of these symptoms were then found to be satisfactorily controllable by restriction of the diet to a list of foods that is larger than was the nonallergenic list*

*previous to the first operation.** In the period of nineteen months since the first operation, none of the other allergic symptoms of the patient recurred. However, the blood-pressure varied between a low point of 116/62 on August 20, 1943, and 190/106 on November 27, 1943.

After the left sympathectomy the continued neuralgia and heartburn brought me at last to the conclusion that the operations had served only partially to correct the food allergy and certain foods were eliminated from the diet from time to time. Soon after this there occurred more or less severe attacks of nervousness and anorexia accompanied by tachycardia. These were believed not to be allergic and, in fact, they always disappeared some hours after the administration of an extra quantity of Vitamin B Complex. The dose of this preparation had to be increased from the original 4 capsules daily to 12 capsules daily. From previous experience with this and other patients, it was believed that the essential ingredient required in the additional 8 capsules was the so-called "unknown liver factor, or factors." This belief was confirmed by reducing the daily dose again to 4 capsules and administering a daily quantity of crude liver-extract** equal to the quantity in 8 capsules. There was a later mild recurrence of the characteristic early symptoms of deficiency of vitamin B complex mentioned above, and the daily dose of liver-extract had to be increased to an equivalent of about 300 grams of liver.†

We see that in the first case of food allergy in which the early effects of sympathectomy were studied, those effects seemed to be: (1) a permanent disappearance of some symptoms and a lessening in the severity of other symptoms on an unrestricted diet; (2) an increase in the dietary list that could be eaten without resulting allergic symptoms or acceleration of the pulse. This case seems also to teach that the maximal benefit of the Crile operation is obtainable by the first stage of the procedure.

Study of the four other cases of food allergy that were referred by the author to Dr. Miscall for sympathectomy (all first stage only of Crile's operation) has confirmed the conclusions just mentioned.

The food-allergic history of two of these patients (C. T. and E. A.) has been reported in detail elsewhere.[2] The chief complaint of the other two patients was idiopathic epilepsy. All four were originally sensitive to so many foods that either it was impracticable for them to lead normal lives on the small list of their nonallergenic foods or it seemed impossible to ascertain such a list (M. C. and C. W.).

Case 2.—Mrs. E. A., aged sixty-three. Food-allergic symptoms: severe headaches, gastric pain, physical tiredness, heartburn, gas, colitis (bleeding), neuralgia, nightmares, hypertension.

Since the operation on unrestricted diet there was no heartburn, indigestion nor gastric pain; headaches were mild, and there was less tiredness. The patient remains sensitive to cereals (moderately), cane sugar, beef? (no test since operation),

*The diet at this time consisted of beef, lamb, pork, fowl, milk, oat, rice, cane sugar, tomato, banana. Previous to the operation the patient was shown to be allergic to all foods excepting beef. The pulse range since the operation is 58 to 68.

**This fluid extract of liver was kindly supplied by D. I. Stadden of Lederle Laboratories.

†Patients W. W. F., E. A., E. F. C., A. W. F. experience definite nervousness, depression and anorexia unless they are given daily considerable doses of vitamin B liver-factors. All of these persons are allergically sensitive to some element in the liver extract (beef, pork, et cetera) and suffer marked allergic symptoms after ingestion of the preparation. However none of them is sensitive to yeast and daily doses of one and one-half (E. A.) to four yeast cakes are sufficient to prevent the symptoms of B-deficiency in all of them.

TABLE I. PULSE-RATE RECORD ON FOUR ILLUSTRATIVE DAYS PREVIOUS TO SYMPATHECTOMY
(Case 3)

Time	Pulse	Diet; Symptoms	Time	Pulse	Diet; Symptoms
July 25,1942			July 27,1942		
B. R.	79		B. R.	72	
B	93−	Tomato		−−	Toothpaste
30 m	96	2 eggs	B	102−	Grapefruit
60 m	102	Pumpernickel	30 m	90	
90 m	100	Milk	60 m	93	
			90 m	100	
L	90−	Pumpernickel			
30 m	93	Ham	Mid-A.M.	81−	Milk
60 m	96	Milk	30 m	81	
90 m	96	Tomato	60 m	94	
		Peach	90 m	88	
D	99−	Lima beans	L	99−	Beef
30 m	98	Lamb	30 m	94	
60 m	97	Tomato	60 m	99	
90 m	97	Peach	90 m	93	
		Milk			
		"shaky today"	Mid-P.M.	99−	Pineapple
			30 m	94	
			60 m	99	"shaky"
			90 m	102	
			D	97−	Potato
			30 m	99	
			60 m	97	"very jumpy"
			90 m	96	
			Ret.	88	
July 26,1942			July 28,1942		
B. R.	77		B. R.	62−	"very jumpy"
B	100−	Cornflakes	B	95−	Grapefruit
30 m	102	Sugar (cane)	30 m	82	
60 m	93		60 m	90	
90 m	86		90 m	106−	Major seizure; unconscious 5 minutes
Mid-A.M.	88−	Milk			
30 m	87	"shaky	Mid-A.M.	102−	Milk
60 m	89	all morning"	30 m	102	
90 m	93		60 m	114	
L	90−	Cornflakes	L	77−	Chicken
30 m	95	Sugar	30 m	77	Peas
60 m	93		60 m	90	String beans
90 m	98		90 m	91	
D	82		Mid-P.M.	103−	Pineapple
30 m	85		30 m	110	
60 m	88		60 m	103	
90 m	88		90 m	112	

B. R.=before rising
B =just before breakfast
L =just before lunch
D =just before dinner
30 m =30 minutes after eating

pork, cabbage, orange, nuts, berries and house dust. She can now eat milk, potato and banana, to all of which she was sensitive before the operation. She has had all of her mattresses, pillows and upholstered furniture covered with dust-proof silk, and she avoids almost entirely all of her dietary allergens, taking daily one and one-half cakes of yeast. Since this regime was arrived at her blood pressure has ranged between 128/64 and 140/86, as compared with 198/120 recorded previous to the initiation of her allergic treatment in 1940. All of her other allergic symptoms have disappeared and her weight has increased from 78 pounds just before the operation to 103 pounds. Her height is 5 feet.

Case 3.—C. W., female, aged eighteen. Major diagnosis: idiopathic epilepsy. The patient was referred by her family physician, Dr. Victor Blenkle, Teaneck, N. J.

TABLE II. PULSE-DIET RECORD ON FOUR ILLUSTRATIVE DAYS AFTER SYMPATHECTOMY
(Case 3)

Time	Pulse	Diet	Time	Pulse	Diet
April 5,1943			April 7,1943		
B. R.	56		B. R.	**67***	
B	65—	Pineapple	B	**79*—**	Tomato
30 m	69	Milk	30 m	69	Milk
60 m	64		60 m	69	
90 m	65		90 m	68	
L	62—	Egg	L	65—	Lettuce
30 m	68	Cheese	30 m	69	Tomato
60 m	64	Tomato	60 m	64	Cheese
90 m	66	Milk	90 m	65	Egg
		Prunes			Milk
					Pineapple
D	64—	Chicken	D	64—	Lamb
30 m	70	Cabbage (lemon)	30 m	**75***	Peas
60 m	67	Carrots	60 m	68	Carrots
90 m	67	Milk	90 m	69	Milk
Eve	65—	Orange			Apple
30 m	66	Raisins			Honey
60 m	67	Cheese			
		Tea	Ret.	67	
April 6,1943			April 8,1943		
B. R.	60		B. R.	60	
B	70—	Tomato	B	64—	Pineapple
30 m	64		30 m	66	Milk
60 m	65		60 m	68	
90 m	66		90 m	65	
L	61—	Egg	L	63—	Peas
30 m	69	Tomato	30 m	65	Tomato
60 m	71	Cheese	60 m	66	Apple
90 m	67	Milk	90 m	61	Milk
(shopping)		Pineapple			
		Prune	D	64—	Lamb
			30 m	68	Tomato
D	63—	Hamburger	60 m	71	String beans
30 m	66	Cabbage	90 m	69	Apple
60 m	65	Peas			Honey
90 m	67	Lemon			Milk
		Carrots			
		Milk			
Eve	64—	Grapefruit			
30 m	**74**	**Cane Sugar**			
60 m	**76**				
90 m	**73**				
Ret.	66				

Working in Red Cross

*Recurrent reaction from cane sugar eaten on the previous day.

Her other food-allergic symptoms were canker sores, constipation and physical tiredness. Blood pressure was 122/86.

The first seizure occurred August 9, 1937. There were three other seizures in that year; five in 1938; twelve in 1939; seven in 1940; fourteen in 1941; and seven in 1942 previous to the sympathectomy, which was performed by Dr. Miscall, August 3, 1942, with the concurrence of Dr. Miller, who confirmed the neurological diagnosis. Phenobarbital and later dilantin (3 capsules daily, after meals) had been taken up to the beginning of the allergic treatment. These drugs were then discontinued and they have not been used since. Convulsive seizures had occurred, as indicated above, in spite of the drugs and there were minor episodes, "shakiness," every few days previous to the operation.

Table I shows the pulse-diet record of C. W. on four days previous to the operation. Study of this record did not inspire any hope of discovering a satisfactory diet that would be entirely free from food allergens.

The seizures after the operation on an unrestricted diet were not less frequent

TABLE III. PULSE-DIET RECORD ON FOUR ILLUSTRATIVE DAYS PREVIOUS TO SYMPATHECTOMY

(Case 4)

Time	Pulse	Diet	Time	Pulse	Diet
July 7,1942			July 11,1942		
B. R.	80				
B	80—	Pineapple			
30 m	80	Cornflakes	B. R.	72	Cornflakes
60 m	74	Sugar	B	74—	Pineapple
90 m	76		30 m	78	Sugar
			60 m	76	
L	80—	Lamb	90 m	76	
30 m	74	Peas			
60 m	76		Mid-A.M.	76—	Tomato
90 m	78		30 m	76	
			60 m	76	
D	74—	**Salmon**	90 m	86	
30 m	76	Potato			
60 m	92				
	—	(seizure)	L	78—	Pork chop
	78		30 m	79	Corn
	76		60 m	78	Pineapple
			90 m	78	
			D	78—	String beans
			30 m	82	Potato
			60 m	74	Bread
			90 m	78	
July 10,1942			July 14,1942		
B. R.	72		B. R.	70	
B	78—	Pineapple	B	74—	Cornflakes
30 m	80	Cornflakes	30 m	74	Pineapple
60 m	74	Sugar	60 m	72	Sugar
90 m	80		90 m	72	
Mid-A.M.	80—	Tomato			
			L	72—	Ham
L	80—	**Beef**	30 m	76	Potato
30 m	92	Bread	60 m	74	String beans
60 m	86	Pineapple	90 m	78	Bread
90 m	80				
			D	74—	Pork chop
D	84—	**Eggs**	30 m	74	Potato
30 m	100	Potato	60 m	72	Corn
60 m	84	Corn	90 m	74	Peas
90 m	80	Bread			

(two- to three-week intervals) but they were distinctly milder. This latter change is reflected in the great change in the effect of the patient's previous allergens on the pulse rate. This is seen in the pulse-diet record on a four-day period eight months after the operation (Table II). The patient was found to be sensitive to certain inhalants, which she is able to avoid. Her food allergens now are cereals, cane sugar, potato, fish, dill pickle and cascara.

Her blood pressure since the operation, even on an unrestricted diet, has been somewhat lower than it was before: August 20, 1942—118/80; September 3—116/80; September 11—116/74; September 16—98/68; September 24—112/66; October 17, 108/66; November 10—106/56.

Since the identification of the listed allergens there have been no seizures excepting on the very few occasions when one of those allergens was eaten. The other food-allergic symptoms have disappeared.

Case 4.—M. C., female, aged seventeen. Chief complaint—convulsive seizures; began at the age of five, occurring at first at six- to twelve-month intervals In the last five years the seizures averaged one each month. More recently there have been three severe attacks in rapid succession. Other symptoms: indigestion, dizziness, constipation, neuralgia, physical tiredness.

The pulse-controlled dietary analysis was begun July 7, 1942, and ended July 21.

TABLE IV. PULSE-DIET RECORD ON FOUR ILLUSTRATIVE DAYS AFTER SYMPATHECTOMY

(Case 4)

Time	Pulse	Diet	Time	Pulse	Diet
February 25, 1943			February 27, 1943		
B. R.	61		B. R.	68	
B	65—	Egg	B	67—	Apple
30 m	69	Baked apple	30 m	65	
60 m	64	(No sugar)	60 m	68	
90 m	66		90 m	70	
L	66—	Beef	L	64—	Beef
30 m	68	Potato	30 m	67	Potato
60 m	67	Beets	60 m	66	Mayonnaise
90 m	69	Mayonnaise	90 m	68	
D	68—	Potato	D	69—	Beef
30 m	70	Carrot	30 m	71	Potato
60 m	67	Tomato	60 m	68	Beets
90 m	69	Mayonnaise	90 m	70	Lettuce
		Apple			Tomato
					Mayonnaise
February 26, 1943			February 28, 1943		
B. R.	62		B. R.	68	
B	64—	Apple	B-L	69—	Apple
30 m	66	Egg	30 m	70	Bacon
60 m	68		60 m	66	Eggs
90 m	65		90 m	68	
L	69—	Potato	D	68—	Beef
30 m	70	Carrots	30 m	70	Potato
60 m	67	Beets	60 m	68	Lettuce
90 m	69		90 m	69	Tomato
					Mayonnaise
D	70—	Potato			
30 m	70	Tomato			
60 m	68	Beets			
90 m	66	Mayonnaise			

The patient was examined July 14, at Rockland State Hospital, by Dr. J. A. Miller, who concurred in the major diagnosis of idiopathic epilepsy and approved the suggestion that she be referred to Bellevue Hospital in New York for sympathectomy by Dr. Miscall.

Table III shows the pulse-diet record of the patient on four selected days previous to the operation. Only sensitivity to fish (second test was confirmatory), beef and egg could be detected, yet there were two other seizures in the two weeks of the dietary study at times when all these three allergens were avoided. This suggested sensitivities to other foods frequently eaten, with long continued allergic effect that depressed the reactive mechanism, as in the case of J. G.,[2] preventing excessive acceleration of the pulse and thus making it impossible to identify individual allergenic foods.

The sympathectomy (first stage Crile) was performed August 15, 1942. The pulse rate remained constantly rapid and irregular on an unrestricted diet in the next several months (100 to 88). There was one mild seizure (two minutes) on September 25. The next seizure, also mild and short, occurred on February 8.

On February 13 the dietary analysis was resumed. The minimal rates were then found to be in the low sixties. In the next two weeks milk, cereals, cane sugar and the pea-bean family were identified as pulse-accelerating allergens. There was one seizure (one minute) on February 19, 1943, on which day milk, rice, biscuits (wheat), sugar and peas had been eaten. Occasional violations of the dietary restrictions have been followed by seizures since that date. The patient is now regularly employed.

Table IV shows the pulse-diet record of the last four days of that period. Of interest are the tests with beef, egg and fish, none of which caused an allergic

tachycardia. The pulse-range (61 to 71) is now normal. The other allergic symptoms have disappeared.

Case 5.—C. T. (Mrs. J. N.). A detailed history of this patient (female, aged twenty-six) has been reported.[2] Her chief complaint previous to the operation was severe dizziness accompanied by psychic depression. The neurologic diagnosis was "nervous and emotional instability—incurable." Other allergic symptoms were nausea, diarrhea alternating with constipation, canker sores, neuralgia, marked physical tiredness and "fluttery heart."

The list of this patient's allergens was so large that daily injections of histamine diphosphate were given for the purpose of establishing a tolerance for some of her important minor allergens, especially cane sugar, potato, banana and tomato.

In spite of this measure, however, the patient lost weight and in August, 1942, she underwent a sympathectomy (first stage, Crile-Miscall).

About two months later she became pregnant, having returned to an unrestricted diet and having regained most of her lost weight. In this period and after the birth of her child she has experienced the usual mild symptoms of pregnancy and also occasional slight attacks of dizziness. Her pulse is "usually high—in the nineties." Unfortunately, it has not been convenient for her to coöperate in a post-operative pulse-dietary study.

The favorable results obtained with the lumbar sympathectomy limited to one side, and the failure, in one case, to enhance those results through the more radical procedure suggested the possibility that the maximal anti-allergic effect obtainable with sympathectomy can be secured by means of the still more conservative operation originally used by Adson. It was learned that such an operation, consisting simply of a removal of three lumbar ganglia on one side, was the regular procedure of Dr. Max Danzis at Beth Israel Hospital in Newark, N. J.

Dr. Danzis describes his procedure in one case as follows:

Right lumbar retroperitoneal incision—December 6, 1943; lumbar sympathectomy; three distinct ganglia removed; cigarette drain inserted in retroperitoneal space; incision closed in layers with silk for skin and chromic gut for muscle and fascia.

Note on following day: Reaction good; right foot perceptibly warmer than left; patient retains all fluids and general condition is excellent.

December 13: All sutures removed.

December 16: Out of bed; discharged.

There were no unpleasant after-effects of the operation (particularly no pain, which was annoying in several of the patients on whom the Crile operation was performed) in either of the two patients operated on by Dr. Danzis.

Case 6.—M. A., female, aged eighteen. Suffered gastric pain at the age of six; petit mal began at ten and convulsive seizures began at the age of thirteen, occurring at first at long intervals (one and one-half years, one year, four months) and in the past year about once in four weeks, with no relation to the menstrual periods. An aura (sense of fainting) always gave her sufficient warning to save her from hurting herself by a fall. In the past year she has experienced almost daily petit mal episodes. She and her family suspected food allergy and she avoided egg, milk, beef, berries, corn and tomato; but the seizures and petit mal continued. Other food-allergic symptoms had been canker sores, constipation, urticaria and physical tiredness.

Certain circumstances made it seem necessary to forego the usual pre-operative pulse-diet study, and the sympathectomy was performed by Dr. Danzis a few days after the patient's arrival in Newark on July 6, 1943.

On July 17 the patient ate egg at breakfast and at 6:15 P.M. she had a one-half minute spell of unconsciousness with rigidity while in bed. The maximal pulse rate immediately afterward was 130. Blood pressure at 7:45 P.M. 106/56. Only the following additional allergens were identified:

Cabbage (lunch and dinner, July 26; seizure about one and a half hours after dinner; maximal pulse-rate 98; several minor episodes in the following morning);
Plum (dinner, July 30; no seizure; pulse-rate to 98; extrasystoles);
Melon (two tests; no seizures; pulse-maxima 88, 87, with indigestion);
Tobacco (on two occasions the inhalation of tobacco smoke from a cigarette smoked by a person near by caused acceleration of the pulse to 90 and 92 respectively within a few minutes).

The tests with beef, milk, corn, berries and tomato and a number of other foods resulted negatively.

The daily maximal pulse rate was rarely more than 73; minimum 58. These figures indicated the normal pulse-range for the patient. However, maxima of as high as 83 or more were encountered that could not be referred to the eating of allergenic foods; and occasionally there was a momentary nervous excitement that suggested an abortive petit mal. These signs were believed to represent the effects of some environmental allergen—tobacco smoke or some unidentified inhalant.

For about three months after the operation the patient was satisfactorily employed in an airplane factory. She then returned to her home in Wisconsin and unfortunately could no longer be kept under observation.

The other two cases are of more recent date. Both are in an indeterminate state on account of a sensitivity to as yet unidentified inhalant allergens, which cause occasional seizures in one patient and more frequent ones in the other.

* * *

Miscall and Rovenstine[6] have recently made an illuminating report of their experiences in the treatment of bronchial asthma with sympathectomy. It is of particular significance, in connection with our own interpretation of the therapeutic effects of sympathectomy, that "all patients (treated surgically by Miscall and Rovenstine) had required frequent hospitalization for intractable asthma which had failed to respond to any and all treatment." These cases in general can be recognized as, for the greater part, of the "intrinsic" or "infectious" variety; that is, nonreaginic.

These authors, on the basis of a comprehensive study of the local neuroanatomy and neurophysiology, arrive at the concept that:

"In asthma gross malfunction occurs as abnormal impulses are initiated in the normal pathways. . . . Excessive stimulation of sensory endings in the bronchi excites afferent impulses which travel to the cord in the sympathetics either directly or via the stellate ganglia. After ascending in the cord to the region of the fasciculus solitarius, they stimulate in vagal fibers the efferent impulses of bronchoconstriction. Irritation of other sensory areas may initiate similar reflex constriction. From the mucosa of the nose, pharynx, and larynx afferent impulses follow the olfactory bulb, et cetera."

Consistently, Miscall and Rovenstine believe that the favorable effect of local sympathectomy—severing of the nervous branches issuing from the

stellate ganglia and excision of second, third and fourth thoracic ganglia usually on only one side—is due to the local interruption of the nervous impulses that are held responsible for the reflex bronchoconstriction.

The twenty-one patients who were subjected to the operation, all of whom "have had complete relief of asthma since operation," were selected from among seventy-two that constituted the entire clinical material. All of the twenty-one patients had previously obtained temporary relief through a stellate block (procaine followed by alcohol). Since some of the seventy-two patients were not relieved by the stellate block, one may suspect that the selected twenty-one patients were among the less sensitive ones in the whole group, which might explain the success of the operation unaided by a search for residual allergens. Our own reported experiences with lumbar sympathectomy and the pulse-dietary control of nonreaginic asthma suggest that the relief of this form of asthma by thoracic sympathectomy (Miscall-Rovenstine) may also be due to the modifying effect of the operation upon the nonreaginic food allergy rather than to an interference with the flow of local nervous reflexes. In this connection it is of possible significance that when recurrent headache was a symptom in the cases of Miscall and Rovenstine, this symptom disappeared after the operation.[5]

DISCUSSION

In view of the preliminary nature of this report, discussion of the results should be limited, although the tentative conclusions have some support in the numerous experiences of a number of surgeons who have employed sympathectomy in attempting to relieve hypertension.

Sympathectomy is already known to be sharply limited in its effectiveness in combating hypertension; now it seems also to possess a limited effectiveness in the relief of other food-allergic symptoms.

However, the present analysis of the few instances in which the operation has been used in some of the most severe cases of food allergy that I have encountered indicates that these most difficult, one may indeed say practically hopeless, cases can often be converted by the operation into relatively easy ones.

It should be emphasized that sympathectomy has frequently failed to extinguish or even lessen the allergic effects of inhalant allergens which are sometimes difficult to identify and avoid.

SUMMARY

1. The literature concerning sympathectomy contains indications that this operation favorably modifies familial nonreaginic allergy.

2. The present preliminary study reveals two effects of the operation, which in the few cases observed have persisted for over one and a half years:

(a) Some of the symptoms may be entirely suppressed, others lessened in severity without any dietary restrictions;

(b) Some foods that previously had caused marked symptoms can be eaten after the operation without causing the slightest detectable allergic reaction.

3. The operation seems especially indicated in those cases of severe food allergy that exhibit sensitivity to a large number of important foods.

DISCUSION

En vista de la calidad de éste informe preliminario, la discusión de los resultados deben ser limitados, aunque las conclusiones tentativas tienen un cierto valor en las numerosas experiencias de una cierta cantidad de cirujanos que han empleado la simpatectomía tratando de remediar la hipertensión.

Ya se sabe que la simpatectomía esta limitada en su eficiencia para combatir la hipertensión; ahora parece que tiene una eficiencia limitada para el alivio de otros síntomas alérgicos alimentícios.

En todo caso, el presente análisis de los ciertos casos en que la operación se ha empleado, en unos cuantos de los más intensos de alergia alimentícia que yo he encontrado y se puede decir casos desesperados, pueden convertirse relativamente por intermedio de esta operación en unos bien fáciles.

Se debe hacer la énfasis aquí que la simpatectomía frecuentemente ha fallado en extinguir o lo mismo disminuir los efectos alérgicos de los inhalantes alérgenos que algunas veces son difíciles de identificar y evitar.

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THE PROTECTION OF THE ASTHMATIC PATIENT AGAINST LUNG IRRITANTS

With Special Reference to Chemical Agents Used in Warfare

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ALL observations on the effect of poison gases* were made under experimental conditions or during the last war on casualties among presumably healthy soldiers.

The generally available instructions for the care of casualties in case of gas attacks on the civilian population are based on these observations. However, it is to be expected that in raids on the civilian population the effect of gases will be different and more severe on that part of the population which already suffer from various diseases and ailments, such as: heart disease, tuberculosis and other conditions affecting the respiratory system, especially asthma. Numerically the actually or potentially asthmatic population is estimated to be from 0.5 to 5.0 per cent of the total population.[2] If we assume the lowest figure to be correct, 0.5 per cent, and if only 10 per cent of the actually or potentially asthmatic population should become casualties from an air raid, the load on physicians and hospitals would be serious indeed (namely, 190 cases in a population of 380,000).

Additional and special protection and instructions will have to be devised supplementing those designed for the population in general.

This article is concerned with the probable effect of chemical agents, such as are used in chemical warfare and others which may occur as a result of disaster like fire, earthquakes, et cetera.

Practically all the poison gases likely to be used in chemical warfare are lung irritants. Patients with respiratory diseases, particularly patients with asthma, will be affected differently and more severely than the average population.

The fact that respiratory irritants easily produce severe asthma, and even status asthmaticus is confirmed by the history of many patients. Exposure to various fumes, smoke, and chemical irritants have produced attacks at times when these patients were relatively free from asthma, or, during times of pre-existing asthmatic conditions, severe status asthmaticus resulted from such exposure. This is particularly well illustrated by the observation of a patient who inhaled certain fumes developed by a powder used to open clogged drains. This particular patient leaned over the drain while pouring the powder. The fumes resulting from it were inhaled and produced an attack of asthma followed by status asthmaticus of unusual severity. The initial period was characterized by an almost complete respiratory arrest with profound cyanosis and extreme mental anguish. If

*The term "poison gas" is used as the popular designation of what the military services call "chemical agents," which do not need to be either poisonous or gases.

such a situation should develop during an air raid it is easily seen that grave and lasting danger might result to the patient.

The following description of the properties of gases and their effect on the respiratory tract are taken from the "Medical Manual of Chemical Warfare,"[1] originally published by the Controller of His Britannic Majesty's Stationery Office, and republished in a first American edition in 1941, by the Chemical Publishing Company, Inc., Brooklyn, New York.

The so-called *"choking gases,"* produce, at first, cough and lachrymation and soon thereafter pain in the chest, dyspnea, and later on pulmonary edema. It is obvious that they are dangerous to a patient with a respiratory disease, and in particular to an asthmatic patient.

The *nasal irritant gases* produce sneezing, burning and aching pain in the chest, throat and nose. They too might be expected to precipitate asthmatic attacks in a predisposed individual.

The two most important gases, namely—*mustard gas* and *lewisite,* are both characterized by striking effects on the respiratory passage such as, aphonia and cough, and lung irritations which, if severe, develop into bronchitis and possibly bronchial pneumonia.

Among the *paralysant gases,* hydrocyanic acid is characterized by an early irritation of the nose and respiratory tract. *Nitrous fumes* such as result from the effects of shell burst or bomb burst, in an enclosed space, also produce an irritation of the respiratory tract.

Finally the *smoke and fumes* from explosive or incendiary bombs will produce asthmatic attacks in many asthmatic patients.

If gas masks should become available, patients suffering from respiratory disease should be on a preferred list so they will be able to obtain them at the earliest possible date, as they naturally are by far the most seriously threatened by the effect of lung irritants. However, the wearing of a gas mask by an asthmatic deserves special and careful attention. In fitting patients with respirator masks used during farm labor et cetera, I have observed that they frequently need a period of adjustment, either mental or physical or both, until they become accustomed to the wearing of the respirator without its producing wheezing or respiratory distress. At the time of the first trial few patients are able to wear a respiratory mask for any length of time without developing an attack of asthma even under conditions which ordinarily would not induce asthmatic breathing. The same effect might reasonably be expected from wearing a gas mask. The patient should be carefully instructed in its use and should wear it frequently before the time when it might be necessary for actual protection against gas.

It would be very dangerous for a patient to be exposed to gas, hastily don a gas mask and find that choking and coughing forces him to remove the gas mask, possibly at the time of the greatest need for protection. The

mental factor in such cases will be of great importance, and the recommendation to have the patient take some sedative, at the beginning of the air raid, is based on the hope that the taking of that sedative will subdue the mental excitation common to people undergoing an air raid and make the patient more able to tolerate the wearing of protective equipment. The possibility that an occasional patient might be allergic to some component part of the gas mask has to be kept in mind. It can be decided by actual trial only.

On the basis of these considerations, patients may receive the following instructions, to be followed in case of an air raid:

1. The patient is instructed to get in touch with his block or area warden and notify him of the fact that he is asthmatic so that if gas masks should become available he will be able to obtain one at the earliest possible time.

2. The patient is instructed to carry on his person an identification card, similar to the one given to diabetic patients, on which is clearly specified that he suffers from asthma, and on which there should be a short note indicating what remedies have proved to be effective in his case, such as: adrenalin, aminophyllin, nicotinic acid, etc., and their dosage. It may be well to caution the emergency station against the use of morphine in these patients.

I believe that such an arrangement would greatly facilitate the care of such a patient if he should become a casualty during a gas raid. It would assure that the patient could obtain special and careful consideration if he should be transferred to a hospital. It might be advisable to designate and equip a certain hospital for the care of all asthmatic casualties.

3. Immediately at the beginning of the raid the patient is instructed to take a capsule containing ephedrine and a sedative in a dose which has been found suitable by prior trial for the particular patient. For instance, ⅜ of a grain of ephedrine and ¾ of a grain of nembutal. The patient is instructed to take this capsule at the very first signal and to repeat it within forty-five minutes if the air raid should last for such a period of time.

4. If the patient is asthmatic at the onset of the air raid he is instructed to administer to himself, if he is used to doing so, a suitable dose of epinephrine in oil at the same time at which the sedative and the bronchial dilator is used. One member of the family or household should be familiar with the administration of adrenalin or of adrenalin in oil if the patient should experience respiratory distress later during the raid.

5. The patient is instructed to administer to himself, or have administered adrenalin in a suitable dose, for instance, .5 c.c. of adrenalin one to one thousand, or half a cubic centimeter of adrenalin in oil at suitable intervals; (one-half hour for adrenalin 1:1000, and four to eight hours for adrenalin in oil), if it has become evident that the patient has become

exposed to a lung irritant, poison gas itself, nitrous fumes or smoke from an explosion.

6. The patient is instructed to keep in his house a suitable supply of such medicine which in his experience has proved to be efficacious in the treatment of his asthmatic attacks, such as aminophyllin, or adrenalin in oil so that he may be given adequate relief at the earliest possible time if a physician in an emergency should have to administer to the patient and possibly be not adequately equipped for treatment of his patient.

7. The patient is warned against relying for relief on inhalation of the popular one per cent epinephrine solution. The gas might produce such severe initial choking that the use of the inhaler would be quite impossible, and the wearing of the gas mask, of course, would prevent the use of the inhaler entirely, unless some very special arrangement could be made for its connection. And finally the removal of the gas mask for the administration would, of course, obviate its purpose entirely.

8. The patient should make himself familiar with the official instructions for the protection against chemical warfare, and should follow them intelligently and rehearse them several times in detail.

CONCLUSION

Practically all the gases used for chemical warfare, or the fumes and smokes resulting from aerial warfare or other disasters are lung irritants. The protection of the civilian population in general is well organized; however, the sick population represents a special and particular problem which deserves the attention of the authorities and the physician. The severest and numerically largest problem is represented by patients already suffering from respiratory disease, in particular, asthma. The mental factor in the production of asthma as a result of air raids and other disasters cannot be overestimated. Proper arrangements have to be made to prepare the patient psychologically for such an eventuality. The use of gas masks, of course, would be highly desirable for asthmatic patients, but it is to be remembered that a careful psychological and mental adjustment to the wearing of gas masks is necessary before a patient could hope to find adequate protection from them. If the patient should become exposed to gas or smoke and fumes, undoubtedly asthmatic symptoms will be produced. A procedure has been outlined which should give the patient the maximum possible protection after exposure. The various items have been discussed and the necessary arrangements have been made to have the patient prepare himself for the emergency of a gas raid well in advance of such a happening.

SUMMARY

The special dangers of gas warfare or exposure to smokes and fumes during disasters to patients suffering from respiratory disease, particularly asthma, have been pointed out. A system of protection for such a patient is outlined in detail.

SUMARIO

Se han apuntado los peligros principales causados por los gases en la linea de combate y tambien los de los humos y vapores mientras los resultantes desastres en enfermos padeciendo de enfermidades respiratorias, en particular, el asma. El método como proteger este enfermo se ha delineado en detalle.

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The Presence of Thermostable Inhibiting Factor in the Sera of Patients Treated for Hay Fever by Injections of Pollen Extract

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éste es presente, requiere otra cantidad de antígeno precisa y medida para la neutralización.

This work was done with the technical assistance of Miss Helen A. Flaherty.

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AN UNUSUAL CASE OF SULFATHIAZOLE SENSITIVITY OF THE RENAL TYPE

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The greater majority of the reports of the renal complication following sulfonamide therapy describe renal calculi as occurring during or immediately following a course of sulfonamide ingestion. The following case report differs from these in that the manifestation of sensitivity was associated with blood and urine tests which were negative for the presence of the drug. The symptoms responded dramatically to treatment with intravenous fluids and ureteral catheterization and kidney lavage.

Hellwig and Reed[1] did pathological studies on a patient who died following sulfadiazine therapy. The patient presented a severe anuria and the histological picture of the kidney was similar to that seen in poisoning by bichloride of mercury. Wright and Kinsey[3] reported a series of cases of renal irritation, the signs varying from mild tenderness over the kidney region to hematuria and severe anuria. More recently Weinstein and Adams[2] reported a case of anuria due to sulfathiazole, the patient being relieved by kidney decapsulation. Biopsy studies showed concretions in the renal tubules.

Our patient, a physician, aged thirty-one, had had a history of pyuria of many years' duration supposedly following scarlet fever in childhood. In order to pass a physical examination for the Army, ten days previous to his admission, he had taken sulfathiazole daily, the dose being 2.0 gms. After seven days of this treatment, following a total ingestion of 14 gms., he suffered from a general malaise, mild fever, back pain and a decrease in urinary output. The ingestion of sulfonamide was immediately stopped, his fluid intake increased and sodium bicarbonate given him in an attempt to alkalinize his urine. His condition, however, grew steadily worse.

On admission, the patient appeared acutely ill. There was a slight edema of the eyelids and a fine erythematous rash over the upper chest and shoulders. There was tenderness in the costal vertebral angle and a positive Lloyd's sign bilaterally. His temperature was 104°; his pulse 130; his respirations 34 and his blood pressure 150/75. The physical examination was otherwise negative.

The laboratory studies showed his urine to be turbid and amber with a specific gravity of 1.009. The urinary pH was 4.5. There was a four plus reaction for albumen, a slight trace of sugar and no acetone. The urinary sediment showed 3-6 hyaline and 100-125 granular casts. There were 2-4 pus cells and 5-10 red blood corpuscles and occasional oxalate crystals in each high power field. The urine was negative, by test, for sulfathiazole.

The blood studies showed a red cell count of 5,010,000 for a hemoglobin of 14.5 grams. The white cell count was 14,150, the differential count showing the polymorphonuclear cells to be 82 per cent; with 9 per cent lymphosites; 1 per cent mononuclear cells; 3 per cent eosinophile cells and 5 metamyelocytes. The blood test for sulfathiazole was negative.

A cystoscopy on the following day proved the bladder to be moderately congested and containing 30 c.c. of bloody fluid. The ureteral openings were normal and permitted the passage of No. 6F catheter to the kidney pelves which were irrigated with normal saline. The catheterized urine was negative by test for sulfathiazole.

Because of severe vomiting and hiccoughs, the patient was treated with Levine drainage and sodium bicarbonate irrigations of the stomach. He was given, intravenously, 3,000 c.c. of 5 per cent dextrose solution for six days. Diathermy was applied to both kidney areas during his hospitalization.

The patient's recovery was rapid, the anuria terminating on the sixth day with the passage of 200 c.c. of urine.

Concomitant studies showed that the non-protein nitrogen, which was normal on admission, had risen to 198 by the seventh day, declining to 57 coincidentally with urinary excretion. The blood creatinine level which had risen to 15.8 mg. per cent by the seventh day declined in proportion to the non-protein nitrogen. The urinary output rose to 2400 c.c. by the tenth day and, when the patient was dis-

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THE IMPORTANCE OF VITAMIN C IN BODILY DEFENSES
I. The Anti-anaphylactic Effect of Vitamin C in the Prevention of Pollen Reactions

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The effect of Vitamin C on adverse reactions to drugs is extremely interesting. The effect of ascorbic acid on the sensitivity to neoarsphenamine is well known, and has been repeatedly described.[1,5,9] It is unknown whether the patients exhibiting these actions are deficient in Vitamin C, or whether Vitamin C detoxifies the neoarsphenamine in a well-saturated patient. Recently, I described a case of rheumatic fever that rapidly became intolerant to salicylates and had a low ascorbic acid content of the serum, this patient was quickly relieved of his disability by adequate intake of Vitamin C.[6] This was also shown to be true for several cases exhibiting intolerance to sulfonamides,[7] and more recently to stilbestrol.[8] These experiments have largely been verified.[4]

Holmes[3] recently published evidence that hay fever patients may be relieved of their disability in great measure by giving Vitamin C in large doses, on the average of about 500 mg. per day. More recently, also, he has shown that Vitamin C will also protect against food allergies.[2]

This short communication is concerned with the protection of an extremely sensitive ragweed patient against adverse reactions to pollen injections.

The patient, a woman thirty-five years of age, was markedly sensitive to ragweed pollen, and was given pre-seasonal treatment with pollen antigen (Lederle). When 200 pollen units were given, the patient developed hives all over her body, swelling of the eyes and tongue and marked wheezing. This reaction was relieved in about fifteen minutes by epinephrine. Attempts to increase this amount slightly brought forth increasingly severe reactions.

The following week the 200 pollen units of ragweed were given along with ½ c.c. of sodium ascorbate, (100 mg. in 2 c.c.) in the same syringe. No reaction occurred. Thereafter, at two-day intervals, increasing doses of ragweed pollen were given with ½ c.c. of sodium ascorbate. In addition, 100 mg. of ascorbic acid were given three times a day by mouth.

The patient volunteered that she had not had citrous fruits for many years because of sensitivity to orange and grapefruit. Finally, a dose of 1500 units of ragweed pollen antigen combined with ½ c.c. of sodium ascorbate was given without incident.

Ascorbic acid was thus able to reduce the exquisite sensitivity to ragweed pollen antigen in this patient. It was thought desirable to find out whether this phenomenon was a local effect of ascorbic acid on the pollen antigen. On a ragweed-sensitive patient, the following skin tests were carried out by intradermal injection:

Ragweed .02 c.c.; ragweed .02 c.c. plus .05 c.c. of sodium ascorbate (described above); histamine hydrochloride 1/1000 solution, .02 c.c.; histamine hydrochloride (1/1000 solution) .02 c.c. plus .05 c.c. of sodium ascorbate. There was no observable difference between ragweed and ragweed with sodium ascorbate or between histamine and histamine with sodium ascorbate. Thus, whatever detoxification occurs is not local in nature.

The liver is the site of detoxification for most noxious substances in the body. Usually they are rendered harmless by conjugation in the liver cells. It is certainly by design that the liver, next to the adrenal glands, contains the most ascorbic acid of any organ in the body. The ascorbic acid is undoubtedly one of the substances concerned with detoxification.

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An Unusual Case of Sulfathiazole Sensitivity of the Renal Type

(Continued from Page 230)

charged as fully recovered, on the sixteenth day it had decreased to 1200 c.c. daily. All other signs and symptoms disappeared.

The history, clinical course and blood and urine tests suggest that the patient may have had a true sensitivity to sulfonamides, which acting on the renal tissues caused anuria independently of any possible mechanical effect due to intra-tubular concretions. Despite the high blood non-protein nitrogen and creatinine levels, the patient responded dramatically to conservative measures of intravenous fluid and ureteral lavage. Kidney decapsulation was not necessary.

CONCLUSIONS

A case of renal sulfonamide sensitivity is described, the condition being associated with an apparent tubular sensitivity, causing anuria, not due to tubular concretions. Recovery was complete following intravenous fluids and pelvic lavage. At no time during the hospitalization were the blood or urine tests for sulfonamides positive.

SUPPLEMENTARY NOTE

Since writing this, attention has been called to the report of a case similar to ours by Dr. J. C. McClelland.

A man with otitis media was given 30 grains of sulfathiazole followed by 130 grains of sulfapyridine (15 grains every four hours for six doses). Acute anuria resulted on the second and death on the seventh hospital day. Pathological examination of the kidneys revealed a fibrinoid material in Bowman's capsule and the proximal convoluted tubules; there were no crystals present in the ureters or tubules. The cause of death is thought by McClelland to be a toxin, as yet unknown.

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Editorial

THE CHICAGO MEETING

It seemed incredible, after hearing the notable speakers representing the leaders in clinical and scientific allergy in this country at the first annual meeting, that the American College of Allergists is only eighteen months old.

Never before in the history of allergy have accurate mass statistics been available concerning the incidence and the results of therapy of allergic diseases in the armed forces of the United States. Colonel Sanford W. French (MC) USA and Major Lawrence J. Halpin (MC) AUS, both of the Fourth Service Command with headquarters in Atlanta, reported on a total of 32,046 patients who had passed through sixty-seven allergy clinics in the Fourth Command for a period of one year. Included were 6,842 with poison ivy, 1,785 were civilian dependents of men in uniform, and the remaining 23,419 were military men. Eight thousand one hundred and thirty-nine patients were hospitalized on account of their allergies with a total of 172,455 days in the hospital. It is estimated that in this single Service Command the valuable services of 20,000 men were saved to the Army. There are now eighty-nine allergy clinics operating as parts of station hospitals in the Fourth Service Command alone. Medical men in charge of these stations are selected from a group specially trained in allergy procedures of testing and treating. The laboratory of the Command produces its own allergens and other materials for both diagnosis and therapy, supplying not only the eighty-nine clinics but many more in other Service Commands. Thus, uniformity of diagnostic and treatment procedures with standardized extracts on a vast scale makes for more accurate and uniform statistics.

A representative of the Division of Biologic Control of the United States Public Health Service was present at the meeting of the Committee on Standardization of Allergenic Extracts of the College, and expressed a desire to coöperate and assist as far as possible this important function of the College. Methods of procedure have now commenced in collaboration with the United States Public Health Service for an intensive study of this very important subject.

Commander Marion B. Sulzberger (MC) USNR, New York, representing the United States Navy, gave an excellent résumé of the allergic dermatoses encountered in the Navy, and Dr. Louis Schwartz, Medical Director, U. S. Public Health Service, Bethesda, Maryland, discussed in detail the various offenders producing allergic dermatitis in war industries. The commentators for these papers were Lt. Col. L. E. Leider, Lt. Morris Lieder and Dr. Samuel M. Peck, who presented lively discussions.

At the Saturday afternoon session the physiologic, pathologic and immunologic aspects of allergy were presented by the guest speaker, Dr. Sanford B. Hooker, Professor of Immunology, Boston University Medical School, with scientists well known internationally following, namely, Drs. Arthur F. Coca, Charles F. Code, J. Bronfenbrenner, Mary H. Loveless and E. C. Stakman.

The seven instructional courses, initiating a series of extension graduate courses in allergy by the College, were very well attended. The various phases of allergic diseases encountered in the specialties and in general practice were presented by Drs. Ethan Allan Brown, Louis A. Brunsting, T. Wood Clarke, Jerome Glaser, French K. Hansel, Charles Miller, Marion B. Sulzberger, J. Warrick Thomas, Leon Unger and Orval Withers. Comprehensive outlines of these courses, printed and perforated to fit a standard ring book, were given to all registrants. Copies of these outlines are being sent to all absent members in the Service, complimentary, by a friend of the College.

Relaxation Saturday evening, June 10, consisted of a most enjoyable cocktail hour sponsored by Almay, Inc., followed by a well-attended informal banquet. The feature of the banquet was a unique portrayal of the seasons as a symphony in color, combined with appropriate symphony music, by Dr. Herbert J. Rinkel. At the banquet, announcement was made of the presentation of $300.00 to the College to be used for research in allergy by Allergen-Proof Encasings, Inc., of Cleveland. The presentation of a sum additional to that already given to the College for research purposes by Marcelle Cosmetics, Inc., was also mentioned. Announcement was made of a fellowship in pediatric allergy amounting to $1,500.00, to be presented through the College to the Department of Allergy of the Rochester School of Medicine, Rochester, New York, by Sharp and Dohme.

A very enthusiastic organization meeting of veterinarians and allergists interested in the immunological problems and allergic manifestations of lower animals was held on Friday afternoon, June 9, preceding the regular College session. The classifications of specific sensitivity in lower animals, reaginic allergy in cattle and dogs and serum sickness in rabbits were presented in the form of papers, slides and colored film. Those participating in the program were Moyer S. Fleisher, M.D., I. Forest Huddleson, D.V.M., Lester Reddin, Jr., D.V.M., Robbins Schroeder, D.V.M., Fred W. Wittich, M.D., and F. W. Gehrman, D.V.M.

The officers and members of the College are deeply grateful to all those who participated in making the first annual meeting a great success. The entire proceedings were characterized by a spirit of warm cordiality, enthusiasm, good fellowship and earnestness, which, if perpetuated at subsequent meetings in the years to come, will insure a substantial building of an institution which will bring about unity and rapid progress in allergy.

F.W.W.

Progress in Allergy

Under the direction of ETHAN ALLAN BROWN

INSECTS AND ALLERGY

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In regard to insects and allergy, Vaughan[62] writes that since classical anaphylaxis was first produced by the parenteral administration of foreign proteins and repeated parenteral administration is a feature of its development, one should not be surprised at the recognition of allergic reactions to the bites of insects. The obverse proposition is indeed much more striking.

Anaphylaxis, in the guise of an allergic response to insect stings, had been present in all its classical manifestations and most obvious form throughout all recorded history and any perspicacious scientist who had wished to give it study might have advanced medical science by many years. Neither Magendie nor Richet, although the latter described a case of bee sensitivity, really saw the implications of their supposedly newly discovered facts or their relationships to pre-existent, commonly observed, but previously undefined phenomena. With no word to describe the observed variation in reactions following the biting or stinging of man by insects, the presence of naturally occurring anaphylaxis was ignored until it was artificially produced, named, defined, and classified. Gould and Pyle[23] lists three cases of clear-cut bee sensitivity, one of which occurred in 1811. There are many earlier descriptions labelled as anomalies and curiosities of medicine.

If sensitivity to silk is excluded (only because of its more distant relationship to the silk moth) the literature lists twenty-five or more insects which are direct causes of allergic disease. Their effects may be mediated by stings, bites, contact and inhalation. There are probably many more which cause their response by means of emanations difficult, if not impossible, to identify.

A complete series of studies on "Insects and the Skin" have been written by Hase[25] and reviewed by Hecht[26] who summarizes all the literature up to 1933.

The effects of stinging by bees have often been described in both folklore and medicine as harmless to some individuals but caused multiple and varied effects in others. Gould and Pyle[25] report Mease as describing fatal reactions in three cases in the early nineteenth century. Beginning at about 1914, the references become more numerous. The papers of workers as Waterhouse,[64] Goss,[22] and Goodman[21] begin more and more to mention the word "anaphylaxis." Reactions, allergic or otherwise, to bee stings are so common that a great many of the cases are probably not reported. Those interested in the many manifestations, both major and minor, of insect stings should consult the admirably detailed work by Beck,[4] who lists many cases of increasing sensitivity due to repeated stings.

Jex-Blake,[29] writing recently, calls attention to the high frequency of bee stings in the area he occupies, reporting two fatalities. His reports of these cases, occurring in 1942, are typical of many previously described. His first patient had been stung four or five times, reacting with the usual transient pain and local swelling. After an interval of ten days the patient was stung again by bees, went into shock and died in two minutes. The second patient had been stung twelve times in twenty years with no ill effects excepting locally. On the thirteenth occasion, following a bee sting in the leg he became acutely ill, cyanotic and unconscious for about ten minutes, suffering an associated involuntary urination and defecation. On

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the fourteenth occasion, nine months later, he was stung again and died within fifteen minutes. Braun[8] describes a patient who was stung by bees on seven occasions, each successive occasion causing more severe reactions, the last sting putting the patient in a coma for four days. Desensitization by bee extract enabled the patient thereafter to suffer bee stings with only mild symptoms.

The responses are not always so typical. Ross[53] mentions an unusual reaction occurring in an apiarist. The patient, a white man, responded to bee stings with a neuritis limited to the stung arm and associated with vertigo, anorexia, thoracic constriction and a generalized fatigue.

The reaction need not follow being stung. The patient may occasionally be sensitive to insect emanations.

Ellis and Ahrens[16] describe three patients whose bronchial asthma was caused by air-borne substances, the attacks arising whenever the patients were near objects which had been in contact with bees. One patient had asthma when in a car containing a robe which had been used to wrap a bee-hive for transportation. The second had bronchial asthma while living in the same house with a man who worked with bees. The third had an allergic coryza while working with bees and after four years of this condition developed bronchial asthma whenever in the proximity of hives, frames or dead bees. This patient, when stung by a bee, developed asthma within fifteen to twenty minutes. On the other hand, the odor of bees brought on an asthma attack in six to eight hours.

These patients might have been sensitive to pollen but skin tests with the associated pollens were negative. On the other hand, skin tests with honey and extracts made in saline of whole bees, bee venom, jelly and larvæ were all positive. An extract of bee wings made in saline gave no test. A ten-minute exposure of the patient to a 1:100 saline solution of bee protein sprayed in a small consultation room brought on an asthmatic attack within four to five hours, the symptoms being extremely severe. Other cases, however, have been described as by Gibb[20] in which the patients reacted to the pollens introduced by the bee stings rather than to the venom, the sting itself or to bee proteins.

Benson and Semenov[5] found, however, on microscopic examination, that the stinger was almost entirely free of pollen contamination. In 1930 these workers studied the allergic properties of bee protein. They divided their material into its component parts: the venom, the sting apparatus including its poison sac and the body without the sting apparatus. By a most delicate technique they were able to separate the poison system from the body of the bee and also the sting apparatus free of contamination by pollen. They were able, therefore, to test with pure bee venom; with proteins from the bee sting mechanism associated with some venom protein; with protein from bee bodies and some adherent pollen; with the isolated pollens, and with proteins from honeycombs. With adequate controls they discovered that their patients gave large reactions to the water-soluble fraction of bee sting, and to the bee protein from the stingerless body. There were lesser reactions to the pollens. A portion of the protein from the sting was boiled and gave a lesser reaction than it did in its unheated form. Nonallergic individuals gave uniformly negative results when similarly tested. One patient was successfully desensitized by injections of increasing amounts of the material until he was taking 0.8 c.c. of a 1:100 dilution. On a later occasion he was stung at least twenty-five times with no ill effects and a year later was again stung and presented no unusual reactions.

In 1939, Benson reported further data in a paper describing eleven patients with bee sensitivity of whom seven were given injection therapy. Of these, however, three had strong sensitization to pollen and two, a moderate pollen sensitivity. In one of these patients passive transfer reactions were successful.

Fisher[18] was able to report on a patient who was stung 15 times with no ill effects and on the sixteenth occasion had urticaria and difficulty in breathing. Her sensitivity became so extreme that if another person who had been stung on the finger by a bee rubbed his finger on her skin she developed urticarial wheals at the point of contact. Contact with an old hat of the husband's, who was a beekeeper, gave her immediate asthmatic symptoms. Since each successive exposure caused difficulties which developed more rapidly and became more severe, desensitization was attempted. Following a series of injections of whole bee extract (Lederle Laboratories) the reaction to a bee sting was reduced to an area of redness, six inches in diameter, the associating symptoms being very mild. It was concluded that she had been successfully desensitized.

Prince and Secrest[51] suspected that whole bee extract might act in a heterologous manner. One of their patients, a ten-year-old boy, had been proven sensitive to wasps, to bees, and to ants. He gave a positive intradermal test reaction to whole bee extract and after several months of injection therapy was able to report that he had only slight local reactions to bee stings and to "yellow jackets" and no reaction when being stung by red ants. A second patient, sensitive to wasps and ants, and a third patient, sensitive to wasps and bees, were given the same extract. Taking as a working basis the zoological classification of the four insects mentioned, and the successful response to treatment, the authors concluded that an extract of the bees would hyposensitize human beings against other species of the same entomological suborder.

That bee sensitivity may be extreme is exemplified by the work of McLane.[41] His patient, given an injection of one minim of a 1:10,000 dilution of bee body extract required epinephrine to control the resulting reaction. Injections of the extract were given every two days until a 1:500 dilution could be tolerated. Thereafter, the patient's desensitization was continued by means of the stings of living bees. After five months of treatment, allergic reactions ceased and after four years therapeutic stings weekly during the bee season prevented a reaction and permitted the patient to work safely with bees. He felt that inasmuch as the extract protected his patient from both the bee emanations and the stings that there was therefor an antigenic substance common to both.

That the otherwise allergic patient may vary from the normal in his response to bee protein is noted by Traub.[60] He performed intracutaneous tests on the chests of children over two years of age with a commercial solution of bee venom. He reports that the wheal reaction usually disappears within twenty-four, the erythema, in some cases, lasting up to forty-eight hours. The largest number of reactions, however, occurred in children who suffered from bronchial asthma. It is suggested, therefore, that the test may be used for the diagnosis of allergic conditions.

Starkenstein and Weden[56] set out to prove what other observers had previously stated, and that is, that the action of bee venom when given intravenously was similar to that of the saponins or the sapotoxins. Saponins act by disturbing the distribution of cholesterol which in turn changes the permeability of cellular walls. Since the action of many narcotics is modified by cholesterol disturbances of this type as shown by their reciprocal action when simultaneously administered, the authors used bee venom in the same way. Their experience demonstrated that bee venom behaved like a saponin but they felt, nevertheless, that they had not definitely determined to what extent the action of bee venom was dependent on disturbances of cholesterol distribution.

Flury,[19] Langer[34] and Lyssy[37] have done studies on the chemistry of bee venom. The material injected contains an indol derivative, probably tryptophane, choline, glycerol, phosphoric acid, palmitic and fatty acids and a non-nitrogenous substance resembling saponin. Benson and Semenov[5] state that the venom may contain a histamine-like substance or a dermolysin releasing histamine locally from the skin. The

venom contains a neurotoxin capable of causing extensive paralysis, a hemorrhagin with a cytolytic effect on endothelial cells causing increased permeability of blood vessels and, in addition, a hemolytic factor causing methaemoglobin production.

For the immediate treatment of the acute reaction of the anaphylactic type resulting from the bee stings, epinephrine and ephedrine are indicated. Flury[19] suggests intravenous calcium. He states that mechanical removal of the venom by suction is impossible and that surgical procedures are rarely necessary excepting in cases of edema of the glottis. The removal of the sting is important as is the neutralization of the toxin. Among other remedies varying in their effectiveness are a dilute solution of ammonia, damp table salt rubbed into the area of the sting, magnesium sulphate and ammonium sulphate. Tincture of iodine and potassium permanganate act to destroy the chemical nature of the venom. As a prophylactic measure it is advisable to disinfect the wound with iodine, formaldehyde or a phenol preparation, since bacterial infection of stings is common.

Some of the literature which concerns itself with wasp stings and hornets has been reviewed above with that in relation to bees. Hubert[27] described a patient who had an anaphylactic accident when he had received two wasp stings at an interval of one hour and Mantoux,[39] and Arntzen[2] anaphylactic shock in patients who were stung by wasps. Duke[15] has reported a death due to wasp stings. Lincoln[35] reported on a patient, seventy years of age, who was simultaneously stung in seven places by "yellow jackets." Within a very few minutes the sites became red and swollen and covered with white urticarial wheals. Soon afterwards the face became suffused, the lips and eyelids began to swell and the abdomen and chest became sprinkled with urticarial wheals which quickly became confluent so that before a hypodermic injection of epinephrine could be made ready the torso was a solid urticarial welt, yellow in color. The reaction was associated with nausea and with a swollen tongue and throat. The temperature was elevated for some hours and although the greater part of the reaction was over following an injection of epinephrine, patches of urticaria recurred for three days, especially at night. A concomitant arthritis was improved for a period of four months.

Despite the ubiquity of the common mosquito and the frequency with which human beings are exposed and bitten by this insect, there are few reports in literature concerning mosquito sensitivity. Kemper[31] whose observations on the effect of insect bites are extremely complete notes that certain people become less reactive to mosquitoes with subsequent series of bites, suggesting that immunity may be built up for this type of sensitivity. Hecht[28] quotes the work of Martini who showed that there were small reactions in the newborn but that the reaction for mosquito bites was large in adults and again smaller in those who had been bitten excessively. Brown[9] described an Arthus' phenomenon type of reaction following mosquito bites.

In 1936 Benson[5] reported on four cases of mosquito sensitization and again in 1939 added five more cases to his earlier series. His patients were all of them extremely sensitive, the immediate effect of a mosquito bite being a wheal several centimeters in diameter with a red, hot, swollen and painful forty-eight hour reaction associated in some cases with cough and prostration.

A simple, buffered-saline extract of whole mosquitoes gave, by intradermal tests, strong specific reactions in sensitive patients but little or no reaction in the numerous normal controls. Intradermal re-injection of the extract two or more days after the first injection showed abolition of the late reaction but not of the early wheal. Sulzberger,[58] discussing Benson's first paper, stated that it was easier to desensitize patients as far as the late, papular reaction was concerned but that the immediate, or wheal type of reaction was extremely difficult to influence and usually remained constant in spite of all desensitization procedures. All but one of Benson's patients were given excellent immunity by injection therapy.

Chemical studies of the antigen showed it to be soluble in water and in saline but insoluble in alcohol. It was nondialyzable, thermostable, and specific. It was common to all parts of the mosquito's body.

The work of Shannon[54] suggests that relief may be obtained by oral vitamin therapy. He lists ten cases treated with thiamine hydrochloride. One of these, a two-year-old boy whose wheals lasted for several days, received 40 mgms. of thiamine during the day, sleeping all through the night without scratching. Given 60 mgms. of thiamine in three doses on the following day he was bitten by mosquitoes with no reaction. Other patients responded similarly. Shannon offers no explanation of the mechanism by which thiamine renders people repellent to mosquitoes. Some of the patients suggested that it might be due to a characteristic odor emanating from their skins after large doses of vitamins because the insects hovered over them and, alighting temporarily, finally flew away. On the other hand, a patient who applied a 3 per cent ointment of thiamine on uncovered surfaces was not protected from insect bites.

For the development of our knowledge regarding allergic reactions to fleas, the papers of Cherney, Wheeler and Reed,[11] and McIver and Cherney[40] should be consulted. In 1939, Cherney and his associates noted that many people in and about San Francisco were "immune" to flea bites. Newcomers, however, lacked such immunity. The authors prepared an extract from fleas collected from dogs and skin-tested a number of individuals. The control solution was prepared with dog serum and with the insecticides used to kill the fleas before collection.

Intradermal tests were done with the solution, a positive reaction appearing within two hours and consisting of a diffused redness, swelling and induration which lasted about two days. A wheal with or without pseudopodia which disappeared within thirty minutes was termed a negative reaction. The first paper described a group of nine individuals who had a definite history of susceptibility, all of whom showed positive reactions. Of eighteen so-called immune individuals, fifteen gave negative reactions and three gave mild, positive tests. At that time the authors noted that their chief difficulty lay in preparing an extract which would not produce positive intradermal tests in patients who were immune. They felt, however, that injection therapy resulted in good immunity for susceptible patients.

Two years later, the series had grown to sixty-seven patients who were treated with an antigen prepared from both the dog flea and the human flea. The extract was used in a dilution of 1:1000 for testing, the injection therapy using a dilution of 1:5000. The course of treatment consisted of six injections. The authors state that after desensitization the wheal produced by a flea is smaller in size, shorter in duration and less irritant. The patients reported in addition that they no longer found fleas on their persons or in their clothing. By 1943 the series had grown to 128 patients, of whom 115 had been relieved of their symptoms, the antigen had also been distributed to 41 physicians for clinical trial on an additional 92 patients who "demonstrated a true allergic reaction to flea bites." Patients who responded with asthma or urticaria to flea bites or to contact with fleas were treated with a polyvalent flea antigen. Following injections given subcutaneously or intradermally, only six patients showed mild local or general reactions but in general the administration of flea antigen was reported as giving satisfactory results.

In 1912 Boycott,[7] while working with fleas, observed that patients who reacted to the bite of the common flea failed to react to experimental bites with the rat flea or to the tropical rat flea but, in time, became sensitive to all three. After fourteen years, he retested one of his original subjects who had previously become sensitized to the tropical rat flea in order to discover whether or not there would be a reaction to the rabbit flea. The first bite gave no reaction but in two months the bites by the rabbit flea so sensitized the patient that red papules would appear seven

days after the flea bite. As the patient became more sensitized the latent interval decreased to thirty-six hours.

At a later date, Boycott experimented in a similar fashion with an oriental flea, not found in England. Of his five subjects the only one who responded with a positive reaction had been exposed to the insect while in the Orient. With repeated exposures, however, over a period of seven to twelve days, the other four subjects became sensitive. Working with bed bugs, Hecht[26] was not able to prove acquired sensitivity of this type.

The reactions to bites of the common bed bug, resulting in an allergic type of response and in urticaria, are too well known to require special comment. Detailed studies on the subject have been done by Hecht.[26] Sternberg,[57] however, reports a case of bronchial asthma due to Cimex lectularius. His case report, however, is not clear as to whether the reaction followed insect bites or was mediated by some other mechanism, perhaps inhalation.

His patient, thirty-seven years of age, had had seasonal asthma for twelve years, the attacks occurring during the second week in July and lasting until the end of September. Intradermal skin tests with pollens, inhalants, and foods were all of them negative. The condition was limited to his home environment. Inspection proved his bed to be infested with bed bugs. Experimental exposure while away from home caused a recurrence of his asthma. An extract of bed bugs in a 1:1000 solution gave a strong intradermal reaction. The sensitivity was transferable to a number of nonsensitive patients and gave negative skin test reactions in sixty hay fever and asthma patients used as a control. When his bedding was changed frequently the attacks ceased completely and the following year when he was given a new bed, new pillows, and sheets free of insect infestation his attacks did not return, the patient remaining in good health.

A similar case was described by Jimenez-Diaz[30] whose patient had had typical asthmatic attacks for ten years. Her symptoms occurred at the beginning of the warm season, lasting all summer and until the end of September. Testing with the usual extracts gave negative reactions. The patient reacted, however, with a very marked positive skin test to an extract of Cimex lectularius with a constitutional reaction several hours later. There was a positive passive transfer reaction. The injection therapy caused constitutional reactions which were minimized by using epinephrine. The elimination of the insects from her household and a course of injections gave the patient complete tolerance.

Churchill[13] in 1930 described urticaria due to bed bug bites, and, from the author's experience and from personal communications from other internists, it would seem that urticaria from this cause is much more prevalent than is commonly supposed.

Our knowledge concerning the cutaneous reactions due to the body louse has grown in the same way as that due to other insects. Nuttall,[46] writing in 1917, considered that anaphylaxis might be a cause of the skin reaction to bites by the body louse. Swellangrebel and Otto[59] had noted some three years earlier that following a louse bite there was a slight hyperemia which lasted for an hour with no itching. When the louse was crushed, however, the spot became reddened, edematous and itchy and occasionally progressed to necrosis. Moore[43] and his collaborators felt that the feces were not the cause of the inflammatory reactions. It remained, however, for Peck[49] and his associates to see the various relationships and prove the reactions to be anaphylactic in type. They were able to show that in most people there was little pain or itching following an initial feeding by the louse. Repeated exposures, however, at daily intervals result in a hypersensitivity which appears in seven to ten days. The skin reactions are of two types, the purpuric and the inflammatory phases, the first due to the bite itself and the second to the associated hypersensitivity. After hypersensitivity develops, continued exposure increases its degree.

A test antigen, made from the head of lice and from the feces, showed the latter to be the causal substance.

Deer fly sensitivity and desensitization were reported for the first time, in 1943, by Mease.[42]. His patient who had been exposed to deer fly bites for two years had, at first, had no particular reaction but with the passage of time responded so markedly that a single bite on the hand caused a swelling of the entire arm. An extract made in buffered saline of macerated flies was used for desensitization. The patient was given a course of treatment on two successive years and at the time of writing had been free from any reaction, excepting for a slight, transient wheal, for four years.

Morrow[44] was able, similarly, to treat patients sensitive to chigger bites. The patients who were tested with an antigen prepared from the chiggers reacted to 0.1 c.c. injected intracutaneously, the positive skin reaction varying directly with the degree of clinical sensitivity. The antigen could be partly destroyed by heat. One of the patients gave positive tests and also passive transfer reactions. The skin of control patients, not sensitive to chigger bites, was insensitive to the antigen. Yeager and Wilson[68] recently wrote a paper on the topical treatment of chigger bites. Named Circa 42, their compound contains n-butyl-p-aminobenzoate 100 Gm. benzyl alcohol 170 c.c., anhydrous lanolin 20 c.c., cornstarch 640 Gm., sodium lauryl sulfonate 64 Gm., and benzyl alcohol for proper consistency. Applied externally it relieved itching in thirty of thirty-two patients who suffered from the pruritus due to chigger bites, mosquito bites, poison ivy and fungus infections.

Duke[15] in his discussion of a paper on May fly hypersensitivity by Figley[17] stated that he had observed a case of sensitivity to the common house fly. In his patient, the "bite" of a house fly would cause a delayed inflammatory reaction at the site bitten. This was followed by a debilitating systemic illness associated with loss of weight if the fly bites were numerous. The author had found no other reference to house fly bite sensitivity. House flies had, however, previously been reported as a cause of nasal allergy.

Jamieson[28] described a patient who responded with violent fits of sneezing whenever house flies were buzzing about her face, causing so great a coryza that she was in the habit of carrying a fly swatter during the fly season. Her skin test sensitivities included wheat, house dust, farm dust, potato and cocoa. The skin tests performed with a moistened fly's wing rubbed into a scratch gave a marked reaction within fifteen minutes. Several hours later the patient presented a red inflamed area an inch and a half by two inches wide at the site of the test. On retesting there was a similar marked reaction. A passive transfer experiment was successful on three occasions.

A small fragment of fly placed on the conjunctival border of the outer canthus of the eye for thirty seconds resulted, within a few minutes, in smarting at the site of application and, within 15 minutes, in a swelling of the lower lid and injection of the corneal vessels at the test site. Half a wing brushed inside the nostrils caused sneezing at once and rhinorrhea within a few minutes. A number of nonallergic individuals tested directly with the same material did not react. The author stated that it was evident from the history and the positive scratch, intracutaneous and passive transfer tests and direct testing, that the house fly might be a cause of nasal allergy.

The effects of the bite of the "black widow" spider are not usually considered an allergic phenomenon. Blair[6] dramatically describes the results of a spider bite upon himself. Among other symptoms, he records local pain and swelling and, in addition, generalized abdominal pain, thoracic constriction, rapid and labored respiration, with a gasping inspiration and sharp, jerky expiration, accompanied by an uncontrollable loud, groaning grunt. Other signs and symptoms resembled histamine intoxication which he suggests were due to the possibility of the presence of a histamine-like ingredient in the venom of the spider as evidenced by the contraction

of the bronchial and intestinal musculature and the symptoms of acute prostration and collapse. The symptoms resembled those due to crotalin (rattle-snake venom) which has a physiological action resembling histamine. The clinical picture, he writes, might well be mistaken for a perforated peptic ulcer, acute pancreatitis, a ruptured ectopic pregnancy, a diabetic crisis, a ruptured appendix with generalized peritonitis, or a renal, or biliary, colic.

More recently, however, the War Office of Great Britain[63] has published a bulletin on the effect of the "black widow" spider as found in North Africa, describing among other effects of the toxin, pain, local edema, inflammation, and urticaria. A sufficient number of cases had evidently occurred to make it necessary to warn physicians in the war areas to exclude the bite of the "black widow" spider in making a diagnosis for conditions associated with the symptoms described.

The emanations of other insects have been described as causing bronchial asthma. In 1935 Ludmer[36] reported on asthma caused from the emanations of locusts. In 1938 Weil[66] investigating summer hay fever of unknown origin in Alabama, described Tanytarsus as the cause of the patient's symptoms. There were positive skin tests to an extract and by passive transfer reagins were proven to be present. The patient was relieved of his symptoms when he was away from the dam at which he worked and during the winter season, excepting when exposed to insects removed while cleaning the dynamos. Treatment with extract of Tanytarsus gave marked relief. Weil was subsequently able to describe two more cases with the same sensitivity, both of which had positive skin tests and were improved by injection therapy.

In 1940, the same investigator, reporting on forty-seven additional cases of summer hay fever of unknown origin in the Southeastern United States, mentioned his investigation on the citrus white fly. These insects appear in April and are common until the first frost, being found in large numbers near and around privet and Euonymus bushes, being so minute they can pass through window screens. Their wings are covered with delicate white scales which are easily shed. The insect is distributed over the Southeast and infests an area corresponding very closely to that in which is found the summer hay fever of "unknown origin."

In 1938, Kern[32] described the first case of bronchial asthma due to sensitization to a species of mushroom fly. His patient, a physician aged 62, had asthma each spring and fall and personally volunteered the information that his symptoms seemed to be present at a time when mushroom flies were numerous. An intradermal test with 0.02 c.c. of an extract of the flies made with Coca's solution and containing 0.33 mg. of nitrogen per c.c. resulted in an irregular wheal, 25 mm. across, with a surrounding zone of erythema 80 mm. wide. The positive skin test was accompanied by a mild constitutional reaction and wheezing. The same test on three control subjects was clearly negative. It was discovered that the patient gave positive skin tests with the extract in successive dilutions down to and including an extract containing 0.00001 mg. of nitrogen per c.c. There were strong passive transfer reactions proving the presence of specific reagins.

Injection therapy starting with 0.1 c.c. of an extract containing 0.000001 mg. of nitrogen and carried through to 0.6 c.c. of an 0.01 extract gave the patient marked relief for that and the season of the year in which the report was made.

In 1941, Sheldon and Johnston[55] reported a case of hypersensitivity to beetle emanations. Dermestid beetles used for removing the flesh in zoological specimens caused rhinorrhea and bronchial asthma in a museum curator who was exposed to them. There were strong cutaneous and passive transfer tests.

In the same year Way[65] reported upon a patient with bronchial asthma sensitive to a small crustacean, the water flea, which, used as a fish food, caused symptoms as an inhalant. The patient presented positive cutaneous and passive transfer tests. His asthmatic attacks ceased when the use of the water fleas as fish food was discontinued.

In the same year, Urbach and Gottlieb[61] described the first case of sensitivity due to clothes moths. Their patient, who had had bronchial asthma for nine years, the symptoms being purely environmental and nonseasonal, lived in a house which was heavily infested with moths in so great a number as to resist the efforts of professional exterminators. Scratch tests with powdered moth gave a strong positive urticarial reaction with a marked erythema, being negative in the control patients. An inhalation test with triturated moths caused nasal stenosis, sneezing, coughing and bronchial asthma.

The patient was injected with moth extract and his home was cleared of moths. Nine months later he was reported as having been entirely free from bronchial asthma.

Our knowledge of moth sensitivity dates back to the work of Caffrey[10] who, in 1915, observed that people working with the New Mexico range moth developed an allergic coryza and wheezing. Some responded with an urticaria due to contact with the caterpillar spines, their reactions becoming more severe with each succeeding season. The subject of moth sensitivity is not free of controversial details.

In 1929 Parlato[48] reported on the first case of allergic coryza and bronchial asthma due to emanations from caddis flies. His patient gave large skin and passive transfer tests to an extract made from caddis flies, the control patients not reacting.

In 1932, Balyeat[3] published his statistical studies on insect emanations, a count being made of butterfly scales by the same technique used for counting pollen grains. On one day in Oklahoma City, the number of such scales on each slide had reached 1,100, which is many times greater than all the pollen grains in the air at that time. Moth and butterfly scales were used for the routine testing of seventy-nine asthma and hay fever patients of whom one gave a very large reaction and another a reaction less large. The remaining seventy-seven patients were skin test negative to the same extract. The patient giving the largest reaction was sensitive also to silk which is, of course, a product of insect metabolism.

In 1932, Parlato[48] proved definite relationship immunologically between caddis flies, moths and butterflies and stated that a patient sensitive to one could be considered as sensitive to the others. Using the passive transfer technique he was able to show that caddis fly extract exhausted the sites for moth and butterfly reagins.

In 1929, Figley[17] had reported the first case of sensitivity to May fly. Four of his patients had seasonal hay fever and asthma, two of whom were given specific treatment with favorable results. In 1934 MacDermot[38] reported a case in Canada. For a description of the life, structure and characteristics of the May fly, Figley's first paper should be consulted.

In 1938, Parlato[48] again reported on his studies extending over a period of seven years. Of 589 patients with seasonal hay fever, nineteen gave repeated positive skin test reactions to the extract of May fly and of these, seven or a little over 1 per cent could really be considered hypersensitive. The other 11 skin test positive patients were considered as reacting nonspecifically. Three of these skin test positive cases were treated with very encouraging effects.

Soon aftrwards, Figley[17] extended the number of patients tested to 1,284 of whom 7 per cent reacted to May fly extract with positive skin tests. A typical patient suffered from a seasonal coryza or bronchial asthma beginning in the latter part of May and extending until the first of August. The patients given specific treatment by injections of May fly extract reported excellent results. Figley felt that the species specific antigen were possessed in common by both May fly and caddis fly. Despite the fact that Parlato and Figley had felt that the caddis fly and May fly had common antigenic properties, Osgood's work[47] however, seemed to prove that there was an immunological distinction between the various species of caddis flies. By means of exhaustion of passive transfer sites he demonstrated that there was a difference in the skin test reactions and assumed the difference to be due to

the fact that only one antigenic substance was present in *Macronema Zebrata* where there were two antigenic fractions in *Hydropsyche Chlorotica.*

Duke[15] in his discussion of Figley's paper[17] noted that the sensitivity described by Parlato was due to the scales of the caddis fly while those described by Figley were sensitive to fragments of the dry pellicles of the May fly. In his discussion of the same paper Figley mentioned that he had tested his patients with moth and butterfly extract as well and had failed, so far, to get a reaction. At the present date the problem, therefore, still requires solution.

For those interested in knowing whether or not the caddis fly is an antigenic agent in the area in which they work a report of the distribution of the caddis fly was published by LaDuca and Durham.[33]

In 1934, Randolph[52] confirmed Caffrey's[10] work on the sensitivity to New Mexico range moth caterpillar. His patient had been exposed for four years to range moths and to their parasite flies. His first symptoms were coryza and sneezing, developing into nocturnal dyspnea and wheezing. Tests for the common pollens in his vicinity were negative. Skin tests, with extracts made from the dust of the floor of the incubation cages in which the parasitization of the eggs of the range moth with the parasite fly occurred, were positive as was the skin test with a May fly extract furnished by Parlato. Therapeutic injections with an extract of the combined larvae and eggshell dust and May fly extract caused constitutional reactions, two of which were mild and one fairly severe. Each intradermal injection caused an urticarial welt 3 cm. in diameter and a swelling of the arm several inches long, the reaction lasting for two days. Soon after the injections were started the nocturnal coughing and wheezing ceased and a very definite improvement of the rhinitis was noted. During the following summer and fall the injections were given at intervals of three weeks, the patient acquiring an excellent immunity.

Of thirty hay fever patients used for controls, two showed a 2-plus reaction and the others did not react at all. One other patient who had been working for two years under the same conditions began to show slight hay fever symptoms and was found to give a 4-plus reaction to the extract.

It would seem from this work that there was a common antigen to the range moth and to the May fly and that injection therapy for this type of sensitivity was successful.

A history of sensitivity to acari extends back over thirty years to a report by Phillipson[50] who reported on the case of dermatitis pruriginosa due to the insect acarus (Pediculoides Ventricosus) infesting Fave Beans. His patients suffered from intense itching and urticaria, supposedly due to an irritating substance deposited by the insect in the skin or by the insect bite itself. Ancona[1] in 1923 reported on an epidemic of asthma occurring among the patients handling infested grain and probably due to acaria and in 1926 Grove[24] reported further cases of asthma and dermatitis due to hypersensitivity to Pediculoides Ventricosus.

More recently, Najera and Dantin[45] stated that 25 per cent of 115 millers, working in non-modern flour mills were found to be suffering from an asthmatic type of respiratory disturbance associated with cutaneous lesions. They felt that both manifestations could be attributed to the presence of acari in the inhaled dust.

Workers with grain and beans have been reported as suffering from a number of conditions. As early as 1912, Chittenden[12] investigated an illness which occurred among handlers of Italian imported broad beans, infested with a broad-bean weevil. The patients complained that the weevils bit them causing a rash and nausea.

In 1928, Dekker[14] reported on asthma and mites and, in this country in a comprehensive study of the nature of various mill dust allergens, Wittich[67] did a comprehensive study as to the nature of various mill dust allergens, reporting on two cases of allergic rhinitis and asthma due to sensitization to the Mexican bean weevil and, in addition, listing the Indian meal moth, the grain and flour mites and the

Psocids or book lice as causing respiratory symptoms in patients associated with the allergens of entomogenous origin in grain mill and feed mill dust. His patients were given careful skin, nasal and ophthalmic tests and the materials were used for passive transfer experimentation as well as for cross testing *in vivo* and *in vitro*. He concluded that a properly selected mill dust would hyposensitize a patient in 85 per cent of the cases if the patient showed clinical and test reactions to the allergens mentioned.

It would seem from this review, which is by no means complete, that entomogenous causes for allergic disease are far from rare. The reactions to stings or bites due to insects are usually easily diagnosed from the patient's history and the physical examination. Those due, however, to insect emanations which may be either seasonal or environmental or both, may be much more difficult to discover. Vaughan[62] lists these as some of the causes of failure in the specific treatment of allergy. Many internists practicing allergy do not routinely test with extracts of insect origin and it is hoped that this review will increase their index of suspicion and stimulate further study in this field. By history and by testing, many more cases of allergic disease due to insects may be diagnosed and also other previously unlisted insects may be discovered as causes of allergic disease.

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OBSERVATIONS ON BACTERIAL ALLERGY IN SCARLET FEVER. Conner, James A., and Milzer, Albert: Illinois M. J., 84:214, (Sept.) 1943.

The authors describe three cases of uncomplicated scarlet fever presenting urticaria during the convalescent period. One patient had two previous attacks of scarlet fever with urticaria appearing with the second attack, although he had received no convalescent serum. Cultures made from the throat and used for skin tests gave positive reactions which were separate and distinct from the Dick toxin tests. The authors feel that these are cases of sensitivity to haemolytic streptococci, which may also be responsible for some of the other sequelae of scarlet fever.

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Eczema—Allergic Dermatitis

A Review of Recent Literature

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A review on eczema must begin with a definition of the term. Yet a generally accepted definition does not exist. The discussion of what we mean when we use this term is very old. With advancing knowledge of the pathogenesis and etiology, many attempts have been made to define eczema more clearly. The results of these attempts have been suggestions all the way from identifying eczema with a single, well-defined, clinical entity, such as contact dermatitis, to attempts to get rid completely of the term *eczema*. This makes it imperative to come to an understanding in regard to the use of the word eczema.

The history of eczema is well worth reading. One has to go back chiefly to the older dermatological masters (Alibert, Hebra) and to the more modern reviews (Alexander,[3] Besnier,[10] Brocq,[16] Jadassohn,[59] Kreibish[64]). There we may learn the value as well as the limitations of morphologic-clinical study; one can also note how slowly new concepts are accepted, how tenaciously even great men cling to pet ideas no matter how erroneous they may be. One should learn especially to become open minded and not to have his field of vision narrowed down by one's own investigations or notions. We must realize that medicine is not an exact science and that terms and definitions are inaccurate, though handy tools. The discussions about eczema have not led to a generally accepted definition. There are hardly two authorities who are in complete agreement. We might get further if we turn away from the historical approach and the lofty constructions and speculations of the specialists and try to define what the majority of the present-day physicians without preconceived ideas mean when they talk about eczema. They probably would fully agree with Hebra's definition: "Eczema is what looks like eczema." That is the answer in a nutshell. It means that the word eczema makes sense only when it is used morphologically. "Eczema" indicates a superficial inflammation of the skin with or without vesiculation, more or less sharply outlined, acute, subacute, or chronic, usually itching at one time or another, and in many instances recurring. This certainly is a broad definition and covers much. Still it is a clinical entity, although a crude one. Naturally, the broader a definition the less meaning it has. But this definition is a practical one and corresponds to what commonly is called eczema the world over. The history of dermatology has amply demonstrated that the term eczema cannot be narrowed down successfully to correspond to a specific entity and to assume greater meaning. On the other hand the practice of medicine has proved that we cannot do without the term eczema. As long as we are not able to classify on a specific etiological basis all the lesions which are called eczema, we shall have to use this word. Furthermore, we need the term eczema as designation until we arrive at a specific diagnosis and for those cases which are caused by a complex etiology. To emphasize again, eczema is nothing more than a morphological term. There is nothing unusual or wrong about employing general diagnostic terms of this sort. In a similar manner we still make use of such diagnoses as asthma, urticaria, anemia, nephritis, pruritus ani, with full knowledge that these "diagnoses" are not etiological entities. For all practical purposes, the term *dermatitis* is synonymous with eczema, although theoretically it is still more general. Frequently, dermatitis is preferred for the more acute, and eczema for the more chronic forms. The term allergic dermatitis would and should apply only to those forms of dermatitis where an allergic mechanism has been demonstrated. Practically, this designation now is usually used in the same wide sense as eczema. It is not a step backward

to encourage the broader use of the term eczema. It is more inducive to investigation to call an eczema of the hands of unknown etiology an eczema, and to admit in this manner one's lack of knowledge. That is also more honest than the widespread habit of labelling those cases, without etiological investigation or proof, a contact dermatitis, a neurodermatitis, atopic dermatitis, or a mycotic eczema, just according to one's preconceived ideas.

CLASSIFICATION OF ECZEMA

No natural system of diseases exists. We can group certain clinical entities under various viewpoints—morphologic, symptomatic, pathologic, or etiologic. Even under any of these headings we can approach diseases from many different angles. Various authors have looked upon eczema from morphological, histopathological, constitutional (functional), endocrinic (nervous), metabolic, or allergic viewpoints and based their classification on one or more of these factors. Morphology is still our only guide in certain forms of eczema, for instance, in seborrheic dermatitis "nummular eczema," some cases of circumscribed lichen simplex. The morphological angle also plays a great role in regard to local treatment. On the other side, etiologic research, especially allergic investigation, has brought the greatest advance in our knowledge of eczema, both theoretically and practically, the most important step being the disinction between atopic and epidermal (contact type) sensitivity.

The enormous confusion that exists today in regard to classification of eczema is well demonstrated by the systems proposed and used by various authors during the last year. The extremes are presented by Lutz[72] and by Rubenstein;[92] a purely morphological classification by the former, an entirely etiological one by the latter. Lutz[72] distinguishes four forms of eczema: (1) Exzema vulgaris. That covers all that is usually called contact dermatitis and also eczema forms of unknown origin. (2) "Epidermitis"—superficial forms of eczema of which he distinguishes an erosive-exudative and an erythematous-squamous type. (3) Dysidrosis, vesicular eruptions of the hands and feet. (4) Tylotic eczema. This covers those chronic forms of eczema characterized by hyperkeratosis and fissures of hands and palms.

Rubenstein[92] presents the following classifications:

I. Venenata: External irritants which produce inflammation in most people all of the time. No phenomenon of hypersensitivity is involved.

II. Toxic: Metabolic (food). Bacterial, fungi, animal parasites. Medicamentosa (drugs internally).

III. Allergic (atopic-metabolic): The true eczema—familial. The hay fever-asthma-eczema complex. Intradermal and scratch tests—positive. Patch test—negative. Passive transfer—positive.

IV. Contact: External irritants producing inflammation in some people all of the time. An acquired local hypersensitivity to any external organic or inorganic irritant. Patch test—positive. Passive transfer—negative.

Classifications on an allergic base are presented by several authors: Vaughan[119] distinguishes between (1) atopic dermatitis, (2) contact dermatitis, and (3) dermatitis medicamentosa.

Urbach[118] proposes the following groups: contact dermatitis (allergic or toxic), neurodermatitis, infantile dermatitis, allergic dermatitis of internal origin, metabolic dermatitis, infectious and parasitic dermatitis, "dermatid" (autosensitization dermatitis).

Lutz[72] emphasizes that we shall not be able to group all existing cases of eczema within our classifications. This applies especially to the etiological ones. In spite of their respective merits, etiological classifications frequently oversimplify the matter and neglect a great number of "eczemas" that—at least at present—cannot be forced into such a system. Another inherent weakness which they share with most allergic classifications is the fact that they are based on different principles, partly on sensitizing mechanisms, partly on allergens. Eczema may be both atopic and caused by a drug or both contact type and caused by an infection.

On the other side, Ormsby and Montgomery[82] who try to do justice to the great varieties of eczema, enumerate the various forms of eczema apparently without any regard to principles, or duplication. Such a presentation appears confusing, but taken as a whole portrays more closely the present status than the more artful and artificial systems. The chief reason for that situation is the particular status of the etiologic investigation of eczema. We are just beginning to understand the etiological background of eczema. Many facts have been uncovered. Many more are still unknown. Problems thought to be solved yesterday reappear today with new doubts. New phenomena, such as autosensitization, contact reactions in atopy, will change or modify older concepts. Interplay and interrelationship of various forms of skin allergy may furnish the key to certain as yet obscure forms of eczema. It seems to me that any classification of eczema must of necessity be unsatisfactory at this moment. Morphology, frequently overestimated by the dermatologist and neglected by the allergist, is still a very important factor. Certain clinical pictures correspond well to etiologic entities. Yet we cannot be guided by morphological criteria alone, because the morphologic appearance, for instance of an eczema of the hand, may not provide the slightest clue to its causation, and yet we cannot build only on etiological considerations. The best we can do is to try to understand the underlying principles and use terms that will be of practical value and will enable us to understand each other.

As one must present a review in some order, I have chosen four headings: (1) Atopic Dermatitis, (2) Contact Dermatitis (Epidermitis), (3) Microbic (Bacterial, Mycotic) Eczema, and (4) Other Forms of Eczema.

ATOPIC DERMATITIS

Atopic dermatitis (Sulzberger) embraces all eczemas that are based on atopic sensitivity, in short, all those forms with sensitivity chiefly of the deeper layer or the vascular structure of the skin as manifested by positive scratch or intradermal tests. The most common form of atopic dermatitis is that well-known chronic dry eczema that involves chiefly the flexural surfaces of the body, such as neck, anticubital and popliteal folds, and the face. It consists of more or less sharply outlined patches of infiltrated (lichenized) skin, usually dry and without blisters, and with more or less severe itching. This rather characteristic morphological entity is frequently called allergic eczema or flexural eczema. It corresponds in its common form to lichen simplex chronicus (Vidal) or circumscribed neurodermitis (Brocq[16]), of the dermatologists, in its relatively rare generalized form to disseminated or diffuse neurodermitis. One must not forget that the latter terms are morphological ones: There is no proof that all lesions that were called lichen simplex chronicus are of atopic origin, especially those with single lesions. Yet there exists an unbroken line of transitional cases from single lesions of circumscribed neurodermitis to the ordinary form with multiple lesions and from here to the diffuse, disseminated variety. The word atopic dermatitis is a valuable addition, because it is the only unmistakable term for this form of eczema. For this reason it should be used, regardless whether one agrees with Coca's concept of atopy or not. It seems advisable to reserve the older terms of lichen simplex or neurodermitis for those cases that are not known to be atopic. We must realize that this typical form of atopic dermatitis is not the only form of atopic sensitivity. Disregarding cases of plain pruritus or urticaria, some of which may be combined with atopic dermatitis, there are other forms which produce an entirely different clinical picture. It is well known that atopic dermatitis in infants, the most common form of infantile eczema, frequently presents an acute oozing dermatitis, especially of the face. This picture is different from the dry, chronic form of atopic dermatitis as seen in older children and adults. Yet all the evidence in these children indicates that they are atopic individuals as manifested by family history of atopies, concurrent atopic manifestation of intestinal or respiratory al-

lergy, and later developments of atopic dermatitis of the dry type, asthma, or hay fever. To call this form of infantile eczema contact dermatitis on account of the clinical picture and positive contact reactions seems confusing. Hill's[54] term "atopic dermatitis by contact" should be used. Yet, these circumstances suggest that some form of epidermal sensitivity may play a role in atopic dermatitis. Such a concept of atopic epidermal sensitivity would also help in understanding the exudative forms of atopic sensitivity in adults.

The most common type is usually called "exudative neurodermatis"; that is, a vesicular and eczema-like, more or less grouped, eruption, chiefly occurring on the hands in middle-aged individuals. As a rule it does not present a typical clinical picture and is often mistaken for contact dermatitis or fungus infection (mycotic eczema). Some, like Obermayer[81] separate this form from atopic dermatitis. He calls it vesicular recurrent eczema of the hands (dysidrosis). These forms of eczema play an important role in everyday practice. Stokes and colleagues,[111] in a paper dealing with vesicular eruptions of hands and feet, point out the role of interplay of various factors, and the combination of different sensitivities in the pathogenesis of these conditions. One must constantly think of these cases of infective allergy as well as of atopic and contact allergy and their consequences, local and systemic.

Stokes and colleagues[111] emphasize also the importance of a painstaking study of these cases, both in regard to predisposing and exciting causes. Among the predisposing factors are mentioned: Allergic family background, familial infective susceptibility; personal allergy and pyogenic susceptibility; ichthyotic or dry skin, seborrheic habitus; functional and other disturbances of vasomotor and sweat mechanisms, including hyperhidrosis, red or blue cold hands, skin hydration resulting from high carbohydrate intake, high alkaline ash food intake (especially fruits et cetera). Exciting causes of the original attack and the flares include (1) inoculation and reinoculation with infective agents; (2) development of local or general allergy of infection (phytids and bacterids); (3) ingestion of food allergens; (4) ingestion of drugs (barbiturates); (5) common contacts, such as soaps, medicaments, wool, dusts, oils, plants, physical agents; (6) emotional shock; (7) intercurrent infections. Ballestero and Mob[7] believe wool to be an important factor in atopic dermatitis. These authors considered elimination of contact with wool an essential part of the treatment. The authors used what they believe to be a new method of desensitization: They noted that in some instances, following patch tests at the site of the lesion, the lesion, after a preliminary period of reactivation disappeared. Therefore, they injected an antigen-vaccine intradermally at the site of the lesion. The results were striking. Patches of neurodermatitis as old as nineteen years improved in twenty-four hours, and pruritus usually, after a period of mild exacerbation, disappeared completely within seven days. Cohen and Friedman[24] experimenting with a histamine azo horse protein, have demonstrated: (1) precipitins specific for histamine in sera of patients treated with histamine azo horse protein; (2) *in vitro* neutralization of histamine by the sera of patient treated with histamine azo horse protein; (3) *in vivo* neutralization of histamine as determined by iontophoretic skin tests on patients treated with histamine azo horse protein. This product has now been released as "Hapamine." It has apparently made a favorable impression among dermatologists in regard to its efficacy in atopic dermatitis. The reviewer has noted especially rapid alleviation of the accompanying pruritus. Obermayer[81] stresses the "functional" background in cases of eczema of the hands and in atopic dermatitis in general. In most of these dermatoses the functional factor is not solely responsible; it may form only one link in a chain composed of several causative elements of which the allergic, bacterial and toxic are perhaps the best recognized. Thus, the etiologic situation in the so-called allergic dermatoses is complicated. There is more and more evidence to indicate that hypersensitivity to certain allergens is not a constant phenomenon. The threshold of allergic response may be raised or lowered by the state of emotional tension. Predisposition to functional disorder, like that to allergic response, appears to be constitutional.

Another form of exudative atopic dermatitis may be observed in generalized pruritic dermatitis of the aged. It is apparently less well known that in these cases the clinical picture may resemble more acute or subacute dermatitis than neurodermitis. The exudative forms of atopic dermatitis in infants, adults, and the old, do not fit in with the general idea that atopy means only sensitivity of the vascular

—connective tissue structures, in sharp contrast to the epidermal sensitivity in contact-type dermatitis. There is, however, evidence that the epidermis may also become the shock organ of atopic sensitivity. Peck,[84] several years ago, suggested that a reactivity between fixed antibodies in the epidermis and the allergens probably brings about the changes in all forms of atopic eczema. Albert and Walzer[2] present another report about positive patch tests to oil-free protein antigens from dust, such as silk, wool, and feathers, in atopic children. The significance of this reaction is not completely understood at this time. It differs from the reaction of the patch tests as seen in contact-type dermatitis. Clinically, it consists of grouped vesicular and papular lesions which do not have a tendency to coalesce and do not lead to necrosis or crusting. Histologically the chief changes appear to be below the epidermis, but there is also hydropic swelling of the epithelium. These reactions were found in a great number of atopic individuals, apparently not more frequently in atopic dermatitis than in other forms of atopy. One might recall in this connection that atopic individuals, children as well as adults, frequently present a somewhat similar reaction to patch tests with copper sulfate and nickel sulfate (Sulzberger), the test presenting a clinical picture decidedly different from that of contact-type sensitivity as found in nickel dermatitis from spectacle frames, or wrist watches. These two different forms of reactions cannot, without further study and proof, be accepted as of identical significance (Sulzberger and Goodman[113]). Patch tests with human dander in infantile eczema are reported by Frank A. Simon.[108]

He observed positive reactions in eight out of twelve young children with "eczema." From his description one might assume that the eczema of these children was—at least partially—seborrheic dermatitis; some gave also positive scratch tests to egg or wheat. Simon[108,109] discusses the possibility that this contact reaction to human dander represents the so-called "seborrheic element" of infantile eczema. These children did not give positive scratch tests or passive transfer to extracts from the dander, whereas young adults with atopic dermatitis showed positive scratch tests but negative patch tests. The allergen was not detected in epidermis from the general body surface or hair from the scalp of a new-born infant.

As a rule, the scratch test or intradermal test in atopic dermatitis results only in an immediate urticarial reaction, whereas the natural exposure produces an eczema. There are cases in which delayed eczema-like reactions follow intradermal, less frequently also scratch tests, with dusts, especially feathers, but also foods. This form of reaction may persist for several days up to several weeks and presents clinically a picture very similar to the atopic dermatitis. These forms of reactions deserve more study. Cases which may be mentioned here are reported by Urbach.[118]

In one of them, presented as "allergic dermatitis of internal origin," there were no positive whealing reactions to scratch or intradermal tests. It was, however, possible to transfer the patient's sensitivity passively, and an eczematous reaction appeared twenty-six hours after the passive transfer. Urbach[118] reports another case of a man thirty-seven years old: for ten years he had suffered from a recurrent oozing dermatitis, especially after eating pork. Intracutaneous tests were negative but a passive transfer was successful. The reaction, however, was positive only after twenty-four hours. Intricate sensitization phenomena and passive transfer reactions in allergic light dermatitis are reported by Stephan Epstein[87]; immediate whealing reactions in some instances, delayed eczematous reactions in others.

Considering that there are cases of atopic sensitivity that present only immediate whealing reactions and others in which both immediate whealing and delayed eczematous reactions occur and finally those of Urbach's which present only delayed reactions to passive transfer, further study will be necessary to decide whether they all belong to the atopic group or represent essentially different forms of sensitization. Cataract is a rare complication of atopic dermatitis.

According to Alice Carleton,[21] forty-six cases of cataract and allergic eczema have been reported. The eczema usually begins in infancy but the cataract does

not appear until the second and fourth decade. From her study it appears that all skin diseases associated with juvenile cataract are genetically inherited. Two cases of atopic dermatitis with cataract are reported by McDannald.[75]

The problem of localized sensitivity, so important in contact dermatitis and the so-called fixed drug eruption, but also in atopic sensitivity, deserves more attention.

Mason and Swineford,[78] studying the observation of autopassive transfer (Cowie) have established this phenomenon as an unequivocal fact. In allergic persons autogenous serum was injected intradermally in one or more places. Following intracutaneous injection of pollen to which these patients were strongly skin sensitive, whealing, itching reactions appeared at one or more of the prepared sites. They appeared from one and one-half to five hours after the subcutaneous injections and lasted from one to twenty-four hours. They were elicited in four out of fifteen patients. However, not all of the prepared sites reacted in a given case. In three instances, desensitization of the prepared sites became apparent as manifested by negative reactions to pollen injection that produced wheals on untreated parts of the body. But only in one instance did this desensitization follow a recognized auto-passive transfer. Unfortunately, Mason and Swineford[78] call this phenomenon autosensitization. As stated above, this term is, and should be, used only for sensitization to homologous antigens. The original term, autopassive transfer, is more descriptive and will avoid unnecessary confusion with true autosensitization. The role of local specific sensitivity in allergic light diseases was demonstrated by Epstein.[37]

Infantile Eczema.—Infantile eczema is not a clinical entity. The majority of these cases belong to atopic dermatitis. Most of the remainder are seborrheic dermatitis or a combination of both. Actual contact dermatitis in babies and infants is seen frequently, especially on the legs; but only rarely does it present the typical picture of infantile eczema.

That foods may act as inhalants, and produce allergic symptoms, has been reported. But in the opinion of Horesh,[57] insufficient importance has been assigned to this factor in the management of infantile eczema.

This author reports nine cases, eight of them under two years of age. They were apparently all instances of atopic dermatitis. Itching and/or exacerbation of the eczema occurred in one child in the presence of a fully-dressed fowl and in others when eggs were broken, fish, pork or bacon were fried, or when cabbage was cooked. It is noteworthy that in four cases, eggs were the offending factor. Horesh believed that failure to recognize these antigens in the environment is frequently the cause of unsatisfactory results in infantile eczema. To keep the infants with infantile eczema out of the kitchen when foods are being prepared is sound advice. Horesh[57] also emphasizes that inhalants are an important factor in obstinate cases of infantile eczema. Apparently the opinion that infantile eczema of the atopic type is chiefly a food sensitization is still prevalent. Kesten[63] is of the opinion that infantile (allergic) eczema is primarily a gastro-intestinal food allergy. According to Burdick,[20] milk, eggs, spinach, and wheat are the commonest foods at fault. He reminds that infantile eczema may be caused by inhalants as well as foods. The reviewer's experience has convinced him that in rural areas environmental allergens are at least as important as foods, the most important factors being cattle, horse, feathers, house dust and wool. Burdick[20] lists soap, water, milk and wool as the common contactants that make the eczema patient worse. The results of scratch tests in 50 cases of eczema in children are reported by Farmer.[42] Horse dander, egg white and grass pollens are by far the commonest reaction-producing antigens. House dust produced a reaction in 30 per cent, rye grass pollen in 52 per cent and an extract of mixed feathers in 20 per cent of the cases. Horse dander produced a positive reaction in 50 per cent of the cases. The latter sensitivity appears to be a transmitted hereditary factor, as many of the babies aged under twelve months gave strong reactions. Egg white produced a reaction in 60 per cent, wheat in 17 per cent, cow's milk in 14 per cent and oatmeal in 9 per cent of the cases. According to Simon's[109] interesting report, human dander is an important cause of infantile eczema. Evidence demonstrating the etiological significance of human dander consists of the following:

(1) positive patch tests to human dander (see above); (2) exposure of all children to this material, either from their own scalps or from relatives; (3) prompt clinical improvement following measures to avoid contact with human dander, and (4) reproduction of the eczema at will on previously not involved areas of the abdomen by exposure to human dander. Sensitization to egg white does not necessarily carry with it sensitization to chicken feathers or serum.[81] According to Sulzberger and Baer,[112] this study tends to confirm the opinion that sensitization to egg white may take place in several different ways. Disturbance of absorption of vitamin A in a few cases of infantile eczema is reported by Di Sant' Agnese and Larkin.[30]

Treatment of Infantile Eczema.—No single topical remedy is so beneficial in this condition as a properly prepared coal-tar paste (Combes[25]). The dressings are changed not oftener than every twenty-four hours. Prompt relief of pruritus with large amounts of thiamin chloride (vitamin B), also in infantile eczema, is claimed by Shannon.[102] Satisfactory, though not conclusive, results from vitamin B complex in infantile eczema are reported by Harris and Gay.[50] These authors feel that vitamin B complex in some cases is a valuable adjunct in the treatment of eczema. They treated twenty infants with 2 to 4 c.c. of Elixir of Betalin complex (Lilly) and Elixir Beta Concemin (Merrell) three times a day over a period from two weeks to ten months. Two children treated eleven and thirteen months, respectively, were cured; eleven showed varying degrees of improvement, and the remaining seven showed no change. Sulzberger and Baer[112] were unimpressed with the results of their trials with various vitamins, including vitamin B complex, in infantile eczema. In the reviewer's experience vitamin B complex is a very useful adjunct in both the atopic and seborrhoic form of infantile eczema. The difference of opinion in this matter may partially be a question of dosage. Harris and Gay[50] apparently have been using rather small amounts, the doses given by the reviewer, using a concentrated form (White's Multibeta 15 to 20 drops three times a day) have been about five to ten times higher. Buchanan, King and Hamilton[19] warn against the indiscriminate use of diets in treating eczema, because they may actually do harm by withholding foods which are sorely needed from a general nutritional standpoint.

A severe complication of infantile eczema is that vaccinia-like eruption which now is usually called the varicelliform eruption of Kaposi, also known as eczema herpetiforme (Kaposi) or pustulosis vacciniformis (Juliusburg). Cases are reported by Barton and Brunsting,[8] Connor and Gonce,[27] Pepple, Murrell and Fowlkes,[89] Ronchese[91] and Wenner.[123] According to Ronchese, the condition is very rare. It seems, however, that the lack of reports is more due to the fact that the condition is not too well known. As it is quite an alarming complication, it deserves wider knowledge.

Kaposi's varicelliform eruption is similar in some respects to variola or vaccinia and is characterized by a constitutional reaction of unusual severity (Barton and Brunsting[8]). According to these authors, in fifty of sixty-four cases in the literature there was a background of infantile eczema or atopic dermatitis. On top of a preëxisting dermatitis, usually atopic dermatitis of infants, but also of adults, a vaccinia-like eruption appears rather rapidly. The patient shows signs of a severe infection, high fever. Clinically we find the typical depressed vesiculo-papular lesions of vaccinia, either single or confluent. The whole face may be involved and turn into a swollen, eroded mass. This condition resembles "eczema vaccinatum." However, the latter is a different condition. Eczema vaccination is generalized vaccinia in eczema patients who either have been vaccinated themselves or have come in contact with vaccinated persons. The belief of Combes and Behrman[26] that the vaccinia virus is also the cause of Kaposi's varicelliform eruption is disapproved by recent investigations. Successful vaccination is no protection against the latter condition; moreover, there are records of successful vaccinations in those who have recovered from the disease. Dennie[29] observed a case that was vaccinated with a very positive result after Kaposi's eruption had cleared up: The vaccination took and was followed by generalized vaccinia.

The etiology of this condition apparently has been clarified by recent studies independently undertaken by Brunsting,[18] Lynch[73] and by Wenner.[123] Lynch[73] comes to the following conclusions based on clinical observation of four cases and

experimental demonstration of the herpes virus: The terms Kaposi's varicelliform eruption and Juliusberg's pustulosis vacciniformis acuta probably apply to a group of disorders whose clinical appearance is similar. Of these patients at least some and probably many have eruptions resulting from implantation of the virus of herpes simplex on previously disturbed skin. Wenner,[123] in an excellent study, isolated strains of a filtrable virus from the vesicular fluid of each of four infants and from the brain of one of them at autopsy. These strains were identified by animal experimentation as closely related to, if not identical with, the virus of herpes simplex. The opinion in regard to the response to treatment with sulfonamides is divided.

Sulfathiazole had no influence on the disease in Barton and Brunsting's case. Connor and Gonce[27] observed good results from sulfathiazole in two out of three cases. In two cases of the reviewer's experience sulfathiazole as well as sulfadiazine apparently did not influence notably the course of the disease. The high fever persisted for several days in spite of adequate treatment. Although there is every indication that this condition is a virus disease, yet pyogenic secondary infection apparently plays some role. Connor and Gonce,[27] and Elizabeth Brown[17] stress the importance of this complicating infection which responds favorably to sulfonamides, apparently both in eczema vaccination and Kaposi's eruption. Brown,[17] believes that the use of sulfonamides has been an important factor in lowering the mortality rate.

CONTACT DERMATITIS

(Contact Type Dermatitis, Epidermitis, Contact Eczema, Dermatitis Venenata)

It is customary to distinguish sharply between epidermal (contact type) sensitivity and atopic sensitivity, as shown in the accompanying table:

	Contact Type Sensitivity	Atopic Sensitivity
Shock organ	Chiefly epidermis	Vascular system
Allergen	Chemicals	Proteins
Tests	Patch test	Scratch and intradermal tests
Reaction from test	Dermatitis appearing after several hours to several days.	Urticarial wheal appearing within a few minutes.
Presence of antibodies	Not demonstrated	Demonstrated
Heredity	Not generally accepted	Demonstrated

There are other important differences. Atopic sensitivity apparently is spread through the blood stream, contact type (epidermal) sensitivity through the deeper lymphatics. Hence, no difference in the severity of the scratch test in atopic dermatitis, be it performed close or distant from the eczema. In contact dermatitis, the reaction from a patch test is the stronger the nearer it is performed to the original site; this is well exemplified in nail polish dermatitis. Furthermore, the skin lesions of atopic sensitivity are independent of the nature of the allergen, they look alike whether caused by pollens, dusts, or foods. In contact type sensitivity, the clinical picture is sometimes fairly characteristic for a specific agent, as best seen in poison ivy dermatitis. Theoretically, the difference between atopic and contact type sensitivity may not be as fundamental. According to Feinberg[43] it is not unlikely that contact allergy depends also on constitutional predisposition and that the latter may be hereditary. The possibility of its connection with atopy should not be entirely discarded (Feinberg). I have mentioned above the facts that lead to the assumption that epidermal sensitization plays also a role in atopic dermatitis. On the other side, dermal sensitivity occurs in some instances of contact type dermatitis. In dermatitis due to nickel or chromates, almost regularly, in addition to a positive patch test, an inflammatory delayed reaction can be observed to intradermal tests with 1:50,000 or 1:100,000 dilutions of these metals. Yet

for all practical purposes, for diagnosis, treatment and prognosis, the distinction between eczemas based on atopic sensitivity and those due to epidermal (contact type) sensitization is still of paramount importance.

Contact dermatitis is the most widely used term to designate those forms of eczema that are a manifestation of epidermal, contact type sensitivity, as described above. This condition is also called eczematous dermatitis, contact type dermatitis, dermatitis venenata. As stated above, this type of dermatitis is characterized by its shock organ, the epidermis, but not—as the word contact dermatitis would imply—by the route of the allergen. The general belief that the atopic allergen works from within, and the contact allergen from without, is erroneous. Atopic dermatitis may be caused by external contact with the atopen, for instance in milker's eczema. On the other side, it is well known that "contact dermatitis" may be caused by internal, oral or parenteral absorption of the allergen. A familiar example of internal causation of contact dermatitis is the eruptions following the ingestion of poison ivy or ragweed oleoresins for desensitization. They produce the same clinical picture as external application.

Unfortunately, this viewpoint is going to be lost, as the review of the literature indicates. The word contact dermatitis is defined even by prominent allergists and dermatologists[63,119] to mean dermatitis caused by external contact. This is now the viewpoint of many physicians who are not familiar with the principles underlying this term of dermatitis. If the term contact dermatitis loses its biological sense, it becomes meaningless. One might say, the term has already lost its value. The confusion is so great that Sulzberger and Baer[112] in order to express correctly what they mean, feel forced to use the term of "allergic contact type eczematous dermatitis." It seems to be high time that an unequivocal definite name should be given to this form of sensitivity. For that purpose, I have suggested the term *epidermitis*[38] to designate that form of dermatitis where the epidermis is the chief shock organ and that is characterized histopathologically by spongiosis or intradermal vesicle formation. This is a morphological, pathological term, describing a usually rather well characterized clinical entity. It is well known that this form of dermatitis does not necessarily indicate an allergic response; it may be caused by primary toxic substances such as croton oil. Such an epidermitis cannot be distinguished clinically nor histologically (Miescher) from that caused by allergic hypersensitivity to nontoxic contactants such as novocaine. As far as I can see there is not one form of pathologic response of tissues that is always a manifestation of allergy. It is the underlying mechanism that determines whether a clinical lesion is of toxic origin, such as the wheal from morphine, or of allergic causation, such as the wheal from ragweed on the hay fever victim's skin. The same applies to that form of eczema that has been termed above epidermitis (contact dermatitis). Where this dermatitis is caused chiefly by an allergic mechanism, it should be called allergic epidermitis; when caused by primary irritating substances, it should be called toxic epidermitis. The term epidermitis would indicate the chief shock organ; it is not in use in the Anglo-American literature and, as far as I can see, the term allergic epidermitis and toxic epidermitis have never been proposed at all. It is, however, not important what we call them. The point is only to have one designation which means the same thing to all of us, even if this term should prove none too correct. Urbach[118] distinguishes between allergic contact dermatitis and toxic contact dermatitis. It would seem logical that a review on allergic dermatitis should disregard toxic epidermitis (toxic contact dermatitis). That is not possible for practical and theoretical reasons. First, it is our task to distinguish between the two forms. Second, they are frequently combined, especially in industrial dermatitis. Third, toxic phenomena probably play also a role in allergic epidermitis. N. P. Anderson[5] questions the purely allergic concept of allergic epidermitis.

He reported a case of match dermatitis which could be prevented by the application of a 1 per cent copper sulfate solution, and other experiences that point to a chemical neutralization of the allergen. The fact that the causes of contact dermatitis are chemicals rather than proteins, and in many instances true poisons, leads him to believe that the difference between toxic and allergic reactions is merely quantitative.

In a recent paper Anderson[6] applies his theory to practice and presents ideas and suggestions for therapy in cases of contact dermatitis. The reviewer agrees with Anderson that the toxic factor in allergic epidermitis has been lost sight of. Another fact, mentioned above, also points in that direction, namely, that certain contact allergens, similar to some drugs, frequently produce a rather specific clinical picture. Anderson's viewpoint appears rather one-sided; the difference between a toxic reaction that produces the same changes or nearly so in all subjects, and an allergic sensitization that affects only a small number, after a definite incubation period, showing fluctuations of sensitization and desensitizations, etc., is fundamental. The difficulty in determining toxic or allergic origin of epidermitis is well demonstrated by the manzanillo tree dermatitis. Severe dermatitis from contact with this tree among sixty soldiers in the Canal Zone is reported by Satulsky and Wirts.[94]

The manzanillo dermatitis (Satulsky[93]), is characterized by a severe burning and pain of face and eyes followed by severe conjunctivitis and edema. It is caused by the fruit, leaves, or branches of the manzanillo tree (beach apple). It is apparently not necessary to contact the tree or its fruit directly. The sap of this tree is considered so poisonous that the dew contains sufficient toxin to cause a severe dermatitis. Sulzberger and Baer[112] remark that the sap of this tree may be a primary irritant since there was no record of previous sensitizing exposure on the part of those affected; however, the possibility of sensitization having taken place by exposures to other plants or agents containing a substance in common with the sap of the manzanillo tree cannot be excluded on the basis of the available data. It appears from a very recent paper by Snow and Harley[119] that the sap is the chief irritating substance and that it is a primary cutaneous irritant, having a pH of approximately five. All fourteen men tested gave a positive reaction to the white sap. However, when tested with the green leaf or the beach apple peeling, only eleven and five patients, respectively, gave a positive reaction. That would indicate a combination of toxic and allergic factors. That may also apply to the cases of epidermitis caused by smoke as reported by Landor.[65] The outbreaks of dermatitis among a group of natives were apparently caused by the smoke of the mango tree (mangifera indica). The lumber from this tree was used as firewood.

Combination of toxic and allergic action plays a great role in industrial dermatitis. This term covers all forms of dermatitis seen in the industry; however, the most important groups are epidermitis, allergic, toxic, or allergotoxic. Industrial dermatitis will, therefore, be discussed with contact dermatitis. Most of the papers about epidermitis (contact dermatitis) deal with new or not so new allergens.

Synthetic resins play a great role. In dermatitis from hair lacquer and hair lacquer pads[39,47,83,95] the causative agent is apparently a new synthetic substituting for the scarce shellac. The allergen responsible for the contact dermatitis from underwear finish (L. Schwartz,[86] H. Keil[60]) is a matter of a controversy. Formaldehyde resins are widely used in the industry, especially in the form of the modern synthetic glues or the so-called glue paper (paper impregnated with glue). Irritation from this source has become quite a problem in industry that produce or work with those modern plastics. It is generally known as glue itch by the patient. Markuson, Soet and Mancuso[77] suggest methods of prevention and of control of dermatitis due to formaldehyde resins. Schwartz, Dunn and Peck[99] deal exhaustively with this form of dermatitis.

How difficult the evaluation of some cases of occupational eczema can be is shown by Biram's[12] experience with cutting oil.

Provocation of latent dermatophytids played an important role in his material. Biram contends that the precipitating factor of the latent dermatophytid in

nearly every case is an insoluble oil that has been run in a machine for at least a month. According to S. M. Peck,[85] dermatitis from cutting oils, especially those of the insoluble type, occurs more frequently than any other occupational disease of the skin. The cutaneous eruptions which cutting oils elicit, are usually of the acneform group, but they sometimes cause allergic dermatitis as well. Parkes[88] recommends the following procedure for the pustular type of dermatitis (folliculitis from cutting oils). Frequent washing with soap (where many blackheads are present) with septicide soap. Daily ultraviolet irradiation just short of a first degree burn. Afterwards soaking in Burow's solution and application of a 1 per cent aluminum subacetate, 7 per cent zinc oxide, talcum, petrolatum ointment. Zinc chromate primer was found to account for the great majority of cases of occupational contact dermatitis in the aircraft industry by Hall.[49] In wartime, dermatitis from explosives becomes a serious problem. L. Schwartz[97] reports that contact dermatitis occurs fairly frequently among workers filling primer cups. In most of these cases the trinitrotoluene has been found by patch tests to be the principal cause of the dermatitis. The committee on occupational dermatoses[44] brings an excellent report regarding recognition and prevention of industrial dermatitis. The selection of the proper personnel is one of the most effective means of reducing dermatitis in industry. Whether it is a dermatitis hazard, it seems advisable to exclude from certain occupations, individuals with a history of recent skin disease of the eczema type or those with a history of eczema; further workers with dry or ichthyotic skin. The patch tests have no place in routine preëmployment examination. The personnel should be instructed in minimizing the occupational hazards. Present nonoccupational skin diseases should not be neglected. Seborrheic dermatitis may be the base for the development of an eczematous occupational contact dermatitis. Fungus infections of the feet and groins may predispose to occupational dermatitis, especially in workers handling oil. This paper also discusses protective measures and contains thirteen formulas for protective ointments and cleansing agents. According to Claassen,[23] individuals with dry skin, whether produced by a mild ichthyosis, a vitamin A and B deficiency, or a hypothyroid, should not be employed in sensitizing occupations.

Dermatitis from black cotton socks is reported by Shelton and Bush[196] from shoes by Shaw,[194] dermatitis from marking fluid obtained from the nut of the ral or bella gutti tree by Livingood, Rogers and Fitz-Hugh.[69] The dermatitis is localized usually in the back of the neck, groins, or around the waist line, according to the markings of the shirt or underwear. Epidermitis from Semecarpus Anacardium (Marking Nut) is reported by N. R. Goldsmith,[48] cases due to cashew nutshell oil by Sulzberger and Baer.[112] Contact dermatitis from rubberized covering of a kneeling bench (Prayer's dermatitis) is reported by Braden,[15] from a rubber service mask by Lewe.[68] Contact dermatitis from "leg makeup" in a young woman was traced by Ellis[35] to a red powder described by the manufacturer as "F D_2 (Yellow No. 3)." Contact dermatitis from olive oil, apparently is a rare occurrence. Sutton's[114] patient, a woman sixty-two years of age, suffered from a dermatitis of ten years' duration. No medications other than olive oil had been used. With no treatment except the elimination of olive oil the dermatitis disappeared within a few weeks completely. Dermatitis from carrots has been investigated by Peck, Spolyar and Mason.[86] Cooked carrots from the army ration C gave reactions which were as strongly positive as those with raw carrots. Two cases of nickel sensitivity are reported by Biberstein.[11] The dermatitis originated in both cases in the region where the fasteners of the garters were in continuous contact with the skin for many years. Both patients were women in the climacterium. C. R. Anderson[4] points out that localized sensitivity—long recognized by dermatologists—is occasionally an important factor in contact dermatitis. For this reason the diagnosis of rubber-glove dermatitis has been missed in some physicians. He suggests as tests in these cases the wearing of a cotton glove, with a small hole cut in it, under the rubber glove. If the patient is sensitive, a small patch of dermatitis corresponding to the hole in the cotton glove will appear.

Localized sensitivity probably also plays a part in those cases of nail polish dermatitis that yield negative tests on the arm or back but give strongly positive results on the forehead or side of the neck.

There are numerous reports about nail polish dermatitis.[32,61,62,67,76,107] Unusual locations of this type of epidermitis are legs[90] where the polish was used to stop runners and scrotum.[120] The reviewer has seen this dermatitis on the fingers of a man who used nail polish to cover minor scratches. Vaughan[121] treated a girl that was sensitive both to nail polish and her bedroom furniture; Bowen[14] saw two cases

where ornaments contaminated with nail polish kept the dermatitis going; Rinkel[90] treated a woman who got enough contact with nail polish by selling phonograph records which were handled by female customers. Madden[76] reports a case of nail polish dermatitis that shows that intimate physical contact, such as persons sleeping together, can produce dermatitis from nail polish even though that person does not wear nail polish.

The general belief that patients who are sensitive to one brand cannot wear any nail polish at all, is refuted by Dobes and Nippert.[32] Patch testing thirty patients, they found two sensitive to all brands (apparently sensitive to the lacquer), eight were sensitive to all except two or more colorless polishes. The rest reacted only to some brands. In order to evaluate the patch tests, patients were allowed to wear the brands that did not elicit positive reactions. None showed any recurrence.

Skin Tests.—Sulzberger and Baer[112] present a very valuable guide in regard to patch tests. It should be read in the original. A decision as to whether a particular case is suitable for skin testing and the selection of the proper type of tests to use are the first requisites for successful employment of this method. The authors list common pitfalls, difficulties, and dangers in performing and reading the tests.

According to Sulzberger and Baer there are six principal and practical uses of the patch tests: (1) to help find eliciting agents in contact type dermatitis; (2) to help select medications to which the patient is not hypersensitive; (3) to assist in differential diagnosis between contact type dermatitis and other conditions; (4) to assist in discovering causes of occupational dermatoses; (5) to help investigate articles intended for consumer use for any possible harmful effect on the user; (6) to help in selecting workers most suitable for employment in certain occupations. A valuable table giving the proper concentrations and vehicles for numerous chemicals is included.

Treatment of Epidermitis—In regard to treatment of contact dermatitis it is well to remember Sutton's[114] advice: "The cure of contact dermatitis is a matter of what is kept off the skin, not of what is put on it." According to Murrell,[80] the great basic law of therapy in eczema is: Soothe the acute, stimulate the chronic.

Treatment of acute dermatitis, regardless of etiology, is outlined by Epstein,[40,41] Lutz,[71]; the value of injections of sodium thiosulfate is still a matter of controversy; Mattice, Botvinick and Abramowitz[79] are skeptical in regard to the value of sodium thiosulfate in the therapy of arsenical dermatitis. Calcium seems indicated in hyperacute inflammation. Lutz[71] also considers calcium gluconate less effective in eczema, than in urticaria.

Failure in treatment of eczema of hands and feet, according to Stokes and colleagues,[111] is usually due to (a) one-track view of the case diagnostically or therapeutically, (b) nonadherence by the patient to a tedious and exacting régime, or (c) nonattention to details by physician or patient. Stokes and colleagues recommend systemic and local treatment, the former including dehydration, rest, psychotherapy, allergic study and treatment, and anti-infectious procedures. Among their suggestions for local treatment is listed the crude coal tar paint for subacute eczema of the hands and feet as follows:

Acetone	2.0
Flexible collodium	4.0
Crude coal tar ad	30.0

The importance of such a multiple attack, both diagnostically and therapeutically, cannot be over-emphasized.

If the treatment of eczema fails, the following possibilities should be considered, according to Lutz[71]: incorrect diagnosis, or the addition of a superimposed dermatosis, lack of establishing the offending factors, incorrect treatment or drug sensitivity. Lutz[71] warns against the excessive use of sedatives. They may increase the irritability of the skin and due to the state of somnolence, may cause the patient to scratch more violently. Epstein[40,41] prefers luminal and codeine to other barbiturates or morphine, but warns of the danger of sensitivity to phenobarbital.

The role of soaps in the care of the patient's skin is discussed by Lane and Blank.[66] The skin surface becomes more alkaline than normal after it is washed with water and soap. Using a sulfonated oil in a dermatological ward for over a year, no skin irritations due to the detergent were noted. They also added a sulfonated

oil to the final rinse water of the laundry of a maternity ward. There was definitely less erythema and chafing. Sulzberger and Baer[112] state that the sulfonated oils are not always well tolerated. The "highly-to-be-desired" ideal soap substitute has not yet been found. Sharlit[103] suggests a superfatted soap, containing 10 per cent of free vegetable oil. It was tried successfully in a group of patients who claimed that their skin would not tolerate soap.

Specific therapy of contact dermatitis is still in the experimental stage;[38,117] its use, at the present time, is practically confined to desensitization to plant dermatitis, especially poison ivy and ragweed. A thorough bibliography of desensitization covering also other substances is given by Urbach.[118] An appraisal of the present status of prophylaxis against poison ivy is presented by Ellis.[36]

According to Ellis the prophylactic treatment of poison ivy is still of doubtful or no value. The most promising results are those of Shelmire who uses poison ivy antigen in corn oil orally over a long period of time. Ellis recommends the use of poison ivy tablets as introduced by Gold and Masucci. He reports treatment of five cases. In one case the patient gave a positive patch test reaction to the 1:10,000 dilution prior to the treatment. At the end of the therapy only the 1:20 dilution produced a reaction. This patient's dose was increased to 500 mgms. One patient discontinued treatment on account of disagreeable reaction. Pruritus ani is a persistent and annoying complication. Howell[58] presents an evaluation of nonspecific measures for prevention of poison ivy dermatitis. His experiments belie the general belief that washing after contact with a poison ivy plant is an efficient prophylactic measure. Thorough washing with soap and water will not prevent or mitigate poison ivy dermatitis in extremely sensitive persons even if it is used after one minute. In persons with average sensitivity it will not prevent dermatitis and it will lessen the severity only if used within the first five or ten minutes after exposure, before the quickly-drying oleoresin has completely dried. Neither a 10 per cent solution of ferric chloride right after exposure prevents dermatitis nor 10 per cent ferric chloride ointment before contact. The same was found with sodium perborate ointment. If petrolatum alone was used as a prophylaxis, it caused spreading of the dermatitis. A 10 per cent solution of potassium permanganate may diminish the severity of ivy dermatitis if used within five to fifteen or certainly not more than thirty minutes after exposure. Howell concludes that there is no known topical prophylaxis for poison ivy. Good results with injections of poison ivy extracts in prophylaxis are reported by French and Halpin.[45] Treatment of acute poison ivy dermatitis with poison ivy extract is still a controversial subject.[41] Extremely good results are reported by French and Halpin in a clinical report from the Fourth Service Command. Among 1,851 cases, good results were obtained in 68 per cent and fair results in 18.4 per cent. Most reports from the thirty-two stations stressed the rapidity of local relief by the first or second injections. French and Halpin used alcoholic extracts according to the method of Cooke and Spain in increasing doses. In a control experiment in one station, the hospitalization period for those receiving ivy extract was 8.4 days and for those who did not, 113 days.

MICROBIC ECZEMA

(Bacterial, Mycotic Eczema; Parasitic Eczema)

Microbic Sensitivity.—It is not quite correct to add microbic sensitivity as a third group to atopic and epidermal sensitivity. However, there is one form of microbic sensitivity that seems distinct from both forms, the well-known tuberculin or trichophytin type of reaction (T.T. type). This reaction is manifested as an inflammatory, cutaneous, infiltrated reaction, that usually appears within a few to twenty-four hours and reaches its maximum as a rule after forty-eight hours. This form of reaction is also called delayed reaction. There is reason to believe that the numerous forms of delayed reaction observed after injections of various antigens, such as food, dust, and microbic products are not all the same. Even microbic extracts produce different patterns of delayed reactions. The typical tuberculin or trichophytin reaction presents a rather characteristic picture. Whether it has any relation to the delayed reactions of atopic sensitivity is an open question. Yet it is well known that microbic allergens in addition to this T.T. type of reaction are capable of eliciting also atopic (whealing) reactions as well as epidermal (contact type) reactions. Atopic microbic reactions, manifested by wheals with pseudopods, are relatively common with molds and monilia, and rare with trichophytin and bacteria. They play—at least with our present knowledge—a greater role in respiratory allergy than in eczema. Epidermal (contact type) sensitivity,

especially with trichophytin and oidiomycin plays a role in eczema. In microbic eczemas all three forms of sensitivity may be observed.

No generally accepted name covers the infectious eczemas; there is also neither a common clinical picture nor a common single form of sensitivity. Yet the frequency of infectious eczema in the wider sense, the special problems of microbic sensitivity, are reasons enough to discuss them as a group.

This group has not received the attention it deserves. There are relatively few papers dealing with it, the textbooks, too, give it only scant attention. Clinically infectious eczemas appear under a great variety of pictures; not all of them are characterized by sharply outlined pityriasiform or psoriasiform lesions. Numerous infectious eczemas present just the ordinary picture of eczema and are frequently confused with it.

The etiological investigation is handicapped. Most of the bacterial eczemas are caused by bacteria which may be found on any skin; hence, a culture of Staphylococcus aureus is no definite proof. On the other side, the absence of the bacteria or fungi does not disprove the microbic origin, as we may be dealing with an allergic (so-called) id lesion. The situation is somewhat better in regard to fungi. Finding of pathogenic fungi like Trichophyton or Monilia albicans as a rule establishes the diagnosis although the latter is sometimes a secondary invader. Negative findings again, microscopically and by culture, are so common, especially in fungus infections with allergic manifestations that they do not exclude fungus infection. Tests for skin sensitivity to bacterial and fungus extracts are only of limited value.

The ubiquity of both staphylococci and streptococci explain that the great majority of people react to their extracts. There are, however, sometimes very severe reactions. They give a clue, especially if they are coupled with a focal flare-up, of the original lesion. There is a general pessimism in regard to the value of the trichophytin and oidiomycin (monilia test). According to J. H. Swartz,[115] the value of the trichophytin test is still questionable because it may denote sensitization to a previous infection and does not exactly prove that the present eruption is related to the positive reaction obtained. Swartz, however, considers the test a valuable laboratory procedure in conjunction with the clinical and mycological studies. The oidiomycin test is considered by him as being of no diagnostic value. Downing[34] also considers biological fungus extracts of doubtful value. He reminds us that tests may be negative in the presence of active mycotic findings. In the reviewer's opinion both trichophytin and oidiomycin tests are not as useless as is generally assumed. In cases of eczema due to fungus sensitization the trichophytin or oidiomycin tests may produce a different picture from the ordinary tuberculin trichophytin type of reaction. Instead of presenting a maximum after forty-eight hours, and then fading, the test may change gradually from this form into an eczematoid lesion frequently producing an identical picture to the eczema. This form of reaction seems rather good etiological evidence, especially if it can be repeated with the same results.

Caro[22] points out that the eczematoid picture of dermatophytosis of the foot may be simulated by moniliasis, dysidrosis, pustular psoriasis, pustular bacterid, streptococcic infection, chronic eczema, and psoriasis.

Bacterial eczema is called by most physicians infectious eczematoid dermatitis. This term originally had a more specific meaning. Engman described it as a vesicular or pustular eczematoid lesion which is associated with trauma, infection or with other suppurative conditions. The term infectious eczematoid dermatitis is now used indiscriminately by most physicians to designate eczema that by the appearance of pustules or sharp outlines or associations with other foci suggest a parasitic origin. It apparently covers both eczemas of primary microbic origin, including probably also some fungus infections, and eczemas of other origin which secondarily have become infected. According to Cooper,[28] there is no specific treatment of infectious eczematoid dermatitis, although the introduction of the sulfa drugs marks a great advancement in its therapy.

Elimination of the focus of infection is of primary importance. Staphylococcic vaccine has been found useful by some and worthless by others. It should be given a trial in stubborn cases. Concentrated sulfur pastes (40 per cent precipitated sulfur in vaseline) as recommended again by Abramowitz[1] are at times very helpful in microbic eczemas.

Infectious eczematoid dermatitis frequently becomes complicated by epidermal contact type sensitivities. This applies to all forms of microbic eczema. Perhaps the best known example of such an interplay between microbic and epidermal sensitivity is the fact, known for a long time, that patients with an epidermophytid of their hands are very prone to develop epidermal (contact type) sensitivities, say to soaps and rubber gloves. The interplay of dermatitis from cutting oils and latent —ids has been mentioned above. There is no form of eczema where sensitization to medication occurs more frequently than in infectious eczematoid dermatitis. That is not all. These people apparently have also a greater capacity to develop drug sensitivities to the internal medication of drugs. This has become especially manifest since the frequent use of sulfonamides in this condition.

If we analyze the cases of severe sensitization from topical application of sulfonamides as reported by Livingood and Pillsbury,[70] Shaffer, Lentz and McGuire,[101] we find that pyogenic infection, primary or secondary, plays a definite role. Some authors stress the similarity between the clinical picture of the drug eruption and the original condition. Weiner[122] reminds us that several mechanisms of drug sensitivity may be involved in the production of generalized eczematoid drug eruptions: Contact dermatitis from topical application of sulfathiazole can be established by means of patch testing. In dermatitis medicamentosa, following oral administration or following absorption from topical application, one would expect to find negative patch tests but positive passive transfer reactions (Prausnitz-Kuestner). This was demonstrated by Shaffer, Lentz and McGuire[101] who reported both immediate wheal reactions and delayed tuberculin-type reactions. Hence a negative patch test to a sulfonamide is no guarantee that internal medication of the same drug will be tolerated. These cases have started quite an argument regarding the topical and internal use of sulfonamides in skin diseases. It seems to the reviewer that severe reactions can be minimized, although not avoided, if the physician recognizes the special danger of sensitization in microbic eczemas in general and in infectious eczematoid dermatitis especially. We must not forget that the matter of quantity plays also a great role in allergic eruptions. The higher the concentration of the drug, the larger the skin surface treated with the medication, the more severe the resulting dermatitis. It is not good sense to use sulfonamide ointments over large areas in generalized cases, because the greater part of the eruption is allergic. It should be applied only to the actual area of infectious eczema. Substituting sulfanilamide for topical use instead of sulfathiazole would also appear helpful. Even if sensitization should occur, the patient probably would be able to tolerate internal sulfathiazole, if an emergency should arise.

The frequent combination of microbic and epidermal sensitivity may not be accidental.

In this regard, similarities between the epidermal contact-type reaction and the tuberculin-type reaction may indicate a closer relationship. Both are more severe the closer to the focus they are performed. In a case of trichophytosis on the right arm we would find the trichophytin reaction more severe on that arm, less on the left arm, less on the right leg, and still less on the left leg. Its counterpart in contact-type dermatitis is well known. In both instances skin-sensitizing antibodies in the serum are usually not demonstrable. Furthermore, as mentioned before, intradermal tests in certain forms of contact dermatitis, especially in nickel and chromium sensitivity, produce frequently a delayed reaction of the tuberculin-trichophytin type.

The close relation between microbic sensitivity and other forms of sensitization has long been recognized in regard to seborrheic dermatitis.

Haxthausen[51] offered the hypothesis (1935) that the micro-organisms of the skin may play a part in the pathogenesis of certain allergic cutaneous eruptions,

inasmuch as they represent the foreign protein which, in combination with substances applied to the skin, occasions the formation of complex antigens capable of producing antibodies also to the added simple compounds. The nature of the protein, too, undoubtedly plays a part, since it is known from other experimental work that some micro-organisms exert a better activating effect upon haptens than do others. This latter suggestion may perhaps explain the good soil offered by seborrheic dermatitis, with its mixed flora of micro-organisms, for the development of allergic states in the skin. Stokes and colleagues[111] point out the importance of the seborrheic habitus, as predisposing to phytids and bacterids and to direct fungous and pyogenic infections.

The allergist should be familiar with the clinical picture and the various manifestations of seborrheic dermatitis so as to distinguish it from real allergic forms of eczema, for instance in infantile eczema, and also because it becomes imperative to treat seborrheic dermatitis in those cases where it is an underlying factor. Seborrheic dermatitis is evidently an infectious eczema (Becker and Obermayer[9]). Whether it is caused by Pityrosporum ovale is still a matter of controversy. That allergic phenomena play a role in its manifestation is rather probable.

The typical seborrheic dermatitis is seen in areas involved in seborrhea, namely, the scalp, the face, over the sternum, in the interscapular, umbilical and pubic regions. The lesions are primarily perifollicular papules, which become confluent to form circinate, annular, serpiginous or irregular plaques. These are yellowish-rose-red in color, with loosely adherent, yellowish, greasy scales (Becker and Obermayer).

The predisposing role of seborrheic dermatitis for the development of contact dermatitis is especially well demonstrated in dye dermatitis occurring often in women around the menopause who have been suffering from seborrheic dermatitis for years. Biberstein's[11] patients with nickel dermatitis suffered also from seborrheic dermatitis. Vaughan[119] reminds us that seborrheic dermatitis, as well as low grade streptococcic infection, must be considered in a differential diagnosis of eczema behind the ears when one is suspicious of contact dermatitis from spectacle frames.

It might be permissible to mention here, while discussing "parasitic" eczema, the study by Peck, Wright, and Gant[87] on cutaneous reactions due to the body louse. The investigation of these authors sheds light on the eczematous eruptions encountered in body lice infestation.

Repeated exposure to the body louse will result in the development of a dermal hypersensitivity in the majority of those exposed. The result of the first bite of a body louse is a small purpuric spot, as indication of trauma. According to others[116] it may also be an urticarial wheal lasting for several hours. In the experiments of Peck and colleagues,[87] repeated exposure to louse bites has led after an incubation period of about seven days to sensitization and severe, even generalized dermatitis.

The experiments of these authors may apply also to a larger field, namely, eczematoid lesions observed in scabies and other mite infestations.

Many instances of eczema in scabies (eczema scabeticum) are probably external dermatitis due to treatment, to mechanical irritation or exacerbation of existing seborrheic dermatitis. Some instances apparently cannot be explained on such a basis and suggest strongly specific sensitization to the mite or some of its products.

Eczematoid dermatitis from mite-infested cheese dust is reported by Dowling and Thomas.[33]

The mites were identified as Tyroglyphus longior. Except for a few small urticarial lesions on the forearms of one patient, the eruption in no case suggested a parasitic cause but was characteristic of a dermatitis. In the light of the above reported experiments on lice, one might explain the urticarial lesions as primary toxic effects of the mite bite and the dermatitis as a phenomenon of sensitization.

OTHER FORMS OF ECZEMA

Clinically, there remain many cases of eczema of unknown origin. Some fit clinically into one of the above described forms but cannot be proven to belong to them; others do not lend themselves at present to an etiological analysis and, therefore, are designated by morphological terms, such as, nummular eczema, eczema en plaque, circumscribed lichen simplex, neurodermitis and others. Frequently they are called simply eczema or eczema of the hands, of the ears, of the eyelids, et cetera. These eczemas are much more frequent than one might suppose from the little attention they get in the literature. Whether or not these forms represent etiological entities is not proven, in fact, is rather doubtful. Nummular or orbicular eczema is a morphologic term, covering a group of eczemas that is characterized by more or less round or oral patches. It has been used and abused for many eczemas of unknown origin. Hall[49] emphasizes that contact dermatitis from zinc chromate usually presents itself under the picture of nummular eczema. It is known that epidermitis from soap, epidermophytids, monilids may also simulate it. Nummular eczema occurs frequently on the hands. The negative results of tests in these eczemas does not exclude the possibility or specific allergic sensitization (autosensitization). Isolated patches of circumscribed neurodermatitis are sometimes just localized atopic dermatitis, probably more often so than is generally believed. Hill and Sulzberger[55] believe that lichen simplex circumscriptus is different from, and unrelated to, atopic dermatitis. There are certainly cases that have not shown, as yet, any relation to atopic sensitivity. One form has recently received more attention under the name of keratoderma climactericum.

According to Lynch[74] this disease received little attention before Haxthausen's report and even now is not often considered. Haxthausen applied the term keratoderma climastericum to a distinct clinical picture consisting of circumscribed hyperkeratosis, mainly of the palms and soles, occurring in women in association with the climacteric and accompanied by various general signs and symptoms, of which obesity and arterial hypertension are those most frequently encountered. Three of Lynch's cases were associated with "neurodermatitis" in other locations: it is Lynch's belief that keratoderma climactericum is a form or variant of neurodermatitis; yet there are features which suggest that it should be considered in a somewhat different category. According to Lutz,[72] keratoderma climactericum corresponds clinically to "tylotic eczema." Garbe[46] treated two patients with keratoderma climactericum and each was completely cured. A natural hormone was used for one and a synthetic hormone on the other. Both patients had a history of contact dermatitis. One also had dermographism. Neither had hypertension or obesity or arthritis.

Many cases of eczema, generalized as well as localized patches, are due to sensitivity to drugs. As drug allergy is a topic of a separate review, it will not be discussed here.

Autosensitization, either alone or in combination with other mechanisms, may be a more important factor than is generally assumed. There have been important contributions to this problem. Such a phenomenon, sensitization to products of the patient's own organs in general and of his own skin in particular, has been postulated clinically for years. Whitfield discussed this phenomenon in 1934, under the title "Autosensitization Eczema."

Hecht, Sulzberger, and Weil,[53] are inclined to explain several phenomena observed in eczema, such as, the spontaneous continuation or the spread of eczematous lesions, and the so-called jumping about of the eczema in the following way: At the inception of the dermatosis the skin is damaged, and some of its constituents denatured; the new products are absorbed and antigenic. Thus the individual becomes sensitized to his own skin. The result is that later lesions develop at sites of trauma or inflammation due to the action of antiskin antibodies which react locally with liberated skin antigen. Organ-specific antibodies to organs other than the skin (lens, muscle) had been previously demonstrated (Burke). Hecht, Sulzberger and Weil[53] produced for the first time precipitants to homologous skin in

rabbits by sensitizing them with skin extracts combined with staphylococcic toxin. When homologous skin alone was injected, the antibody formation was questionable. When staphylococcic toxin alone was injected, precipitins against this toxin were produced but not against skin. Hopkins and Burky[56] suggest the possibility of cutaneous autosensitization in eczema of unknown cause. They studied more than fifty patients that had acute, subacute, or chronic dermatitis of the hands and a few of various other parts of the body. The group did not contain patients with known contact dermatitis. Staphylococcus aureus was recovered from the cutaneous lesions of fifty patients. Fifteen of the forty strains of staphylococci were toxin formers. Seven of the patients were tested with Hampton's and Cooke's human dander extract. Six reacted positively. All patients showed a positive reaction to staphylococcic toxin. Hopkins and Burky have treated twice weekly twenty patients with staphylococcic toxin injected intracutaneously who were observed for six months or more. Treatment was given for a minimum period of three months with toxin dilutions of 1:10,000 or 1:1,000. The dose should be gradually increased until there is a focal exacerbation of the lesion or until the local reaction at the site of injections, after twenty-four to forty-eight hours, is about 4x4 cm. In case of focal exacerbation, the dose is reduced. In ten patients the eruption cleared up entirely. The authors emphasize that they have used a staphylococcus toxin prepared by Burky which differs from those produced commercially. Their results, therefore, cannot be compared with those of other investigators who have used different toxins.

In closing, the reviewer must acknowledge that, apart from the papers he has overlooked, a number of contributions to eczema were not available to him, especially from the European literature. The review shows that, in spite of the war, great progress has been made in the field of eczema. Especially important appear to be the contributions on autosensitization, on sensitivity to human dander, to industrial dermatitis and the prospect of a nonspecific-specific therapy of atopic dermatitis and perhaps other forms of eczema by the conjugated histamine antigen (hapamine).

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News Items

HONORARY FELLOWS

Sanford B. Hooker, M.D., Professor of Immunology, Boston University Medical School, the guest of honor at the first annual meeting of the College, and J. Bronfenbrenner, Ph.D., Professor of Bacteriology and Immunology, Washington University School of Medicine, St. Louis, have been elected Honorary Fellows of the College for their meritorious contributions to immunologic research in allergy. Marion Sulzberger, Commander, (MC) USNR, New York, has been elected an Honorary Fellow of the College for his outstanding contributions to dermatologic research in allergy.

OFFICERS ELECTED

At the business session held Sunday afternoon, June 11, at the first annual meeting of the American College of Allergists, Dr. French K. Hansel, President pro tem, was elected President, and Dr. Orval R. Withers, Vice President pro tem, was elected Vice President for the year 1944-45. Dr. Fred W. Wittich was made Secretary-Treasurer for the coming year.

Dr. Leon Unger, F.A.C.P., F.A.C.A., Assistant Professor, Northwestern University Medical School, Attending Physician, Allergy Clinic, Attending Physician, Cook County and Wesley Memorial Hospitals, Chicago, Illinois, has been elected a member of the Board of Regents to succeed Dr. Erich Urbach.

Dr. Harry L. Rogers, F.A.C.A., Chief of the Allergy Clinics of the Jefferson and Cooper hospitals, Philadelphia, has been elected a member of the Board of Regents.

In addition, the following will continue to serve as Regents for the year 1944-45: Dr. Ethan Allan Brown, Major Lawrence J. Halpin, Lt. Col. Tell Nelson, and Dr. J. Warrick Thomas.

It was decided that for another year, during the period of organization of the College, the Board of Regents, upon the recommendations of the Credentials Committee, will continue to elect all members to the College for the year 1944-45.

GRADUATE COURSE ON CLINICAL ALLERGY

Instead of a sectional meeting of the American College of Allergists, preceding the session of the Southern Medical Association, there will be a continuation of the instructional courses presented at the first annual meeting of the College in Chicago recently. This will be an intensive five-day graduate course on clinical allergy, to be given November 4 to 8 inclusive at St. Louis. It will be conducted by experienced instructors composed of men noted for their leadership in allergy. The course will include the necessary practical procedures in the diagnosis and treatment of the various allergic states. The beginner in allergy desiring to become a Fellow in the College and others will find the course most valuable. Each instructor will be allowed an entire half day in which to present his subject when history taking, terminology, etiology, pathogenesis, symptomatology, demonstration of the various methods of testing, special examinations, differential diagnosis and methods and principles of treatment will be stressed. Special subjects will be presented at evening classes.

Further details concerning the course, including the list of instructors, will appear in advertisements in a number of the leading medical journals, and all particulars will appear in the July-August issue of the ANNALS OF ALLERGY.

The charge for the entire course will be $100.00. The Coronado Hotel, St.

Louis, has been selected as the headquarters since it is just outside the loop district and has less distraction.

All those wishing to register for this course will please communicate with Dr. French K. Hansel, President of the American College of Allergists, 634 North Grand Boulevard, St. Louis 3, Missouri.

SOUTHWEST ALLERGY FORUM

Dr. Ralph Bowen, Houston, Texas, was elected President and Dr. George Owen, Jackson, Mississippi, was elected Secretary-Treasurer of the Southwest Allergy Forum at its meeting held in Jackson, Mississippi, April 15 and 16. The meeting place for 1945 will be New Orleans, April 5 and 6.

The ANNALS OF ALLERGY has recently been placed on the exchange list of the Boletin de Instituto Vital Brasil, the official publication of the Instituto Vital Brasil. Excellent summaries of each article appear in English. The publication contains material on investigative and clinical medicine including hygiene, bacteriology, serotherapy, immunology, pharmacology, endocrinology, veterinary medicine, industrial chemistry, clinical analyses and biology. Exchanges of medical periodicals of the South American countries for the ANNALS OF ALLERGY are welcomed.

To complete the College library files, we are desirous of having the May and September numbers for 1931 of the *Journal of Allergy*. It would be greatly appreciated if any members who have these copies would care to contribute them to the library.

Those desiring a photograph taken of the group attending the banquet of the first annual meeting of the College may obtain the same by writing to Dr. Fred W. Wittich, 401 La Salle Medical Building, Minneapolis 2, Minnesota. The cost of the photograph is $1.50.

BOOK REVIEW

PAIN MECHANISMS. By W. K. Livingston, M.D., 253 pages, 26 illustrations. Price—$3.75. New York (11): The Macmillan Company, 1943.

The author and teacher has succeeded in a direct and personal manner in recording his observations of the clinical aspects of pain mechanisms and the interpretation of causalgia.

In the first section of the book, Dr. Livingston discusses the anatomy and physiology of sensory perceptions and pain conduction as a basis for clinical interpretation of complex pain problems. His skill as a neurosurgeon is shown in the second section devoted to clinical cases. The third section deals with interpretations. Many cases of causalgia with its various symptom complexes are resulting from the present world war which will tax the efforts of the internist, the surgeon, the physiologist and the psychiatrist. A search for the functional and organic irritants that cause disturbance of the physiology of the regulatory centers of the central nervous system must be sought and remedied both medically and surgically.

The author has made every effort to correlate our present knowledge of a difficult subject with its practical therapy. F.W.W.

Allergy of the Nervous System

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